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DR. E. LIBMAN, *President.*

BLOOD CULTURES IN TYPHOID FEVER.*

BY ALBERT A. EPSTEIN, M.D.

(From the Pathological Laboratory of Mount Sinai Hospital.)

The principle established by Castellani and Schottmüller concerning the bacteriology of the blood in typhoid fever and the knowledge that we have in positive blood cultures a means of determining early and with certainty the presence of this disease,

*Preliminary studies were presented before the New York Pathological Society in October, 1906.

have induced many investigators to search for methods of facilitating the work. The recent advances have, therefore, been mainly in the line of demonstrating the ease with which the work may be done. But as the literature indicates, the frequency of positive findings is not greater with the new than with some of the old methods.

Much of the difficulty hitherto experienced in cultivating the bacilli has been attributed to the bactericidal power of the blood. To overcome this hindrance, Castellani[1] used large quantities of bouillon and obtained positive results in 78 per cent. of the cases. Schottmüller[2], however, used agar, the blood being present in the proportion of one to three of the medium. He was successful in finding the bacillus in 81 per cent. of the cases.* Numerous other methods have been employed for cultivating the bacillus. Lemiere[3] was successful with cultures made from defibrinated blood. Eppenstein and Korte[4] grew the bacilli in oxalated blood. Müller and Graef[5] observed the growth of the bacilli in the fibrin network of clotted blood. Klodnitzky[6] succeeded in growing the bacilli from blood laked in ordinary sterile water. In twenty-five cultures made in our laboratory, we found multiplication of the bacilli in oxalated blood twenty-three times (without the addition of any nutrient material).

From these data it will at once be seen that the unfavorable influence of the blood upon the growth of the bacilli has been considerably overrated. We can not escape from the fact that with a variety of methods the results obtained by nearly all the investigators have been uniform. It seems that in working with one or another method many of the real conditions underlying the success or the failure of the work have been overlooked.

Thanks to the co-operation of the attending staff of the Hospital, I am able to report on one hundred and fifty-eight blood

*If we adhere to the theory that the blood of a typhoid patient exerts marked inhibitory influence upon the development of the typhoid bacillus, Schottmüller's success in the work must be explained on the hypothesis of Eppenstein and Korte (4): that agar in solidifying destroys or diminishes the bactericidal properties of the blood.

cultures taken in one hundred and thirty-one cases of typhoid fever at different stages of the disease (this series includes two cases of paratyphoid, one of mixed infection with a streptococcus, and one case in which secondary infection by the pneumococcus occurred). The subject matter will be taken up in the following order:

1. A description of the technic of obtaining the blood, and of the media used.

2. The results, a comparison of the advantages of the various media, a note on the characteristic appearance of the colony of the typhoid bacillus in glucose agar, and a note on two cases of mixed infection.

3. The results in relapses.

4. The relationship of positive findings to the presence of the Widal reaction.

5. The relation of the bacteriemia to the stage, course, and severity of the disease.

6. The significance of negative cultures.

7. A note on the possible significance of the bacteriemia in relation to the prognosis.

8. Conclusions.

The method used in obtaining the blood is that introduced into the laboratory by Dr. Libman.[1] The blood is usually withdrawn from one of the veins in the bend of the elbow. In stout patients and in children, in whom these veins are often invisible or too small, a vein on the back of the hand or the dorsum of the foot has occasionally been used. It is wise to inspect these different parts first and see where one can best find a vein of sufficient size. After the constriction bandage has been applied above the part selected, and the field has been scrubbed with soap and water, it is rubbed with ether, alcohol, and, finally, a 1:500 solution of bichloride of mercury. Because a large number of media were used for each blood culture, it was necessary to withdraw

a moderately large quantity of blood, 10 c.c. or more. It will be shown later that although the use of so large an amount of blood increases the chances of obtaining a positive result, a smaller amount is usually sufficient. When the work was first taken up bouillon media were mainly used; later the series of eight media used as routine in the laboratory were employed. In the course of most of the recent work the following eleven media were used.

1. Plain nutrient bouillon (from meat infusion, 0.9 per cent. acid to phenolphthalein*) in flasks containing 120 c.c.

2. Two per cent. glucose bouillon (titer and quantity like medium 1).

3. Plain nutrient agar (0.9 per cent. acid to phenolphthalein).

4. Plain nutrient agar to which ¼ to ⅓ volume of ascitic serum had been added.

5. Two per cent. glucose agar (titer same as that of the plain agar).

6. Two per cent. glucose agar with ¼ to ⅓ volume of ascitic serum.

7. Plain agar (neutral in reaction to phenolphthalein).

8. Five per cent. glycerin agar (0.9 per cent. acid).

9. Ten c.c. of Conradi's bile medium.

10. Five c.c. of Kayser's bile medium.

11. Ten c.c. of a 0.2 per cent. solution of ammonium oxalate.

The work was more or less developmental in character, and was carried on without any preconceived notions concerning the possible merits of one or another medium. (The eight media referred to above as belonging to our routine series were numbers 1 to 8 on the list.) The latest studies were made with media 1, 2, 5, 9, 10 and 11. The oxalated solution was used for two reasons: first, to test the growth of bacilli in oxalated blood

*The titer of 0.9 per cent. acid was chosen because it was found to give a better growth of typhoid bacilli than more acid media.

without the addition of any nutrient material; and, second, to test the efficiency of this solution as an intermediate measure in blood culture work between the bedside and the laboratory.[8] In the use of the bile media, the directions given by Conradi[9] and Kayser[10] were closely followed. In each series, after the blood was withdrawn it was rapidly distributed into the media and incubated at 37.5° C.

The cultures were observed from three to seven days, and careful records were made both as to the time of appearance and the features of the growths. The following summaries give the results obtained with the different media.

SUMMARY No. I.

	Medium	Number of Cultures	Amount of Blood	Positive Results	Negative Results	Result in Percentage	Time in Hours
1.	Plain bouillon.....	81	2 c.c.	61	20	75%	48
2.	2% glucose bouillon	86	2 c.c.	70	16	81.4%	38
3.	Plain agar	31	2 c.c.	12	19	38.7%	50
4.	Plain agar and serum	26	1.5 c.c.	8	18	31%	68
5.	2% glucose agar	83	2 c.c.	67	16	80%	31
6.	2% glucose agar and serum	20	1.5 c.c.	8	12	40%	58
7.	Neutral plain agar	16	1.5 c.c.	1	15	6.66%	——
8.	5% glycerin agar....	32	2 c.c.	12	20	37.5%	68
9.	Conradi (10 c.c.) ...	28	1.5 c.c.	16	12	57.5%	26
10.	Kayser (5 c.c).....	29	2 c.c.	17	12	58.375%	31
11.	Ammonium oxalate solution (10 c.c.) ...	25	3.5 c.c.	23	2	92%	29

SUMMARY No. II.

The Two Bouillons Compared.

Both bouillons used simultaneously in 80 positive cultures.

Both bouillons positive in 51 cultures—63.7%.

Both bouillons negative in 8 cultures—10%.

Plain bouillon positive, 2% glucose bouillon negative, in 7 cultures—8.7%.

Plain bouillon negative, 2% glucose bouillon positive, in 14 cultures—17.5%.

So that in all, plain bouillon was positive in 58 out of 80 cultures—72.5%; and 2% glucose bouillon was positive in 65 of the cultures—81.25%. Total positive results for both bouillons —90%.

The average total amount of blood used for the bouillon media was 4 c.c. per culture.

SUMMARY No. III.

Agar Media Compared.

A. Plain agar, 2% glucose agar, used together in 26 cultures.

Both positive in 10 cultures—38.4%.

Both negative in 3 cultures—11.5%.

Glucose agar positive alone in 13 cultures—50%.

Plain agar positive alone in 0 cultures—0%.

B. 5% glycerin agar, 2% glucose agar, used together in 31 cultures.

Both positive in 10 cultures—30.1%.

Glycerin agar positive, glucose agar negative, in 2 cultures —6.2%.

Glycerin agar negative, glucose agar positive, in 14 cultures —45.16%.

Of the total number of 31 cultures, 2% glucose agar was positive in 24 cultures—77.4%; whereas glycerin agar was positive in 12 cultures—38.4%.

SUMMARY No. IV.

Bile Media Compared.

Both media used in 27 cultures.

Both media positive in 11 cultures—41.8%.

Both media negative in 6 cultures—22.2%.

Conradi medium positive, Kayser medium negative, in 4 cultures—14.8%.

Kayser medium positive, Conradi medium negative, in 6 cultures—22.2%.

In the 27 cultures in which both bile media were used, the total positive results obtained were 21 cultures—77.78%.

The average total amount of blood used for the bile media was 3.5 c.c. per culture.

SUMMARY No. V.

Ammonium Oxalate Solution Compared with Other Media.

Ammonium oxalate solution used in 25 cultures; positive in 23.

A. Ammonium oxalate solution, plain bouillon, used together in 19 cultures.

Growth appeared in the oxalated blood in 17 cultures, and in plain bouillon in 13 cultures.

B. Ammonium oxalate solution, 2% glucose bouillon, used together in 20 cultures.

Growth in oxalated blood in 18 cultures, and in glucose bouillon in 17 cultures.

C. Ammonium oxalate solution, 2% glucose agar, used together in 23 cultures.

Growth in oxalated blood in 21 cultures, and in glucose agar in 20 cultures.

D. Ammonium oxalate solution, Conradi medium, Kayser medium, used together in 13 cultures.

Growth in oxalated blood in 11 cultures, in Conradi's medium in 8 cultures, and in Kayser's medium in 7 cultures.

The average amount of blood used in this medium was 3.5 c.c.

In studying these results we can readily see which media appear to be best suited for the work. We find that the media

can be arranged in two groups, one of which is distinctly favorable to the growth of the bacilli, and another of which is unfavorable. It is evident, of course, that the word "unfavorable" must be used cautiously because in any one blood culture the organisms may be few in number and therefore may appear on some of the media and not on others. In such instances it is greatly a matter of chance which medium gives positive results. The bacterial invasion of the blood in typhoid fever appears to be more uneven than it is in infections by other bacteria, for even in some cases where the bacteria are comparatively numerous, we find that the given amount of blood divided equally into like portions of the same medium gives an unequal number of colonies in each portion. This difference is at times very striking. Müller and Graef in their cultures from clotted blood had the same experience. I am not able to say what the cause of the uneven distribution is; possibly clumping of the organisms plays some part. I have at times found that fully developed colonies of typhoid bacilli (of the type to be later described) would appear on 2% glucose agar within the first sixteen hours of incubation, and then thirty-six to forty-eight hours might elapse before any more colonies appeared on the same plate. We must assume from this fact that as a result of a conglomeration or actual clumping, the respective colonies arise from different numbers of bacilli.

In this connection it may be stated that in the entire series of one hundred and fifty-eight cultures, I have at no time seen so large a number of bacteria in the blood as that observed by Schottmüller and Schüffner.[1] Whether this difference is due to the difference in the type of cases studied or not, we can not determine; possibly differences in technic may account for the discrepancy.

From the study of the variations which occur in the number and growth on the different media and different portions of the same media, I am inclined to the belief that up to a certain degree the media exert but little influence on the result of the culture. The bacilli will grow on any medium provided such a medium is not actually antagonistic. It appears that bacilli fail to grow

well in neutral media and in media the titer of which is above 0.9 per cent. acid. The experiments of Müller and Graef with clotted blood, as well as those of Eppenstein and Korte with oxalated blood, and those of Meyerstein with bile salts, led to the belief that the fluidity of the blood was essential to the development of the bacilli. The later work of Müller and Graef showed that the fluid state of the blood for growth is not necessary, as they observed the growth in the fibrin network of clotted blood.

It is likely that a number of bacilli which reach a culture medium are impaired in their vitality in consequence of the detrimental influences to which they are exposed in the body; so that the blood withdrawn for the culture may contain bacilli few of which, if any, are viable. But the claim so frequently made that the failure of the bacteria to grow is wholly due to the continuation of the bactericidal action of the blood (in vitro) is not supported by experience. The work of Eppenstein and Korte bears evidence to the contrary. They conclude from their experiments that the bacillus develops an immunity against the bactericidal action of the blood of the host. This view gains support from the fact that the bacteria multiply in defibrinated, oxalated, laked and clotted blood without the addition of any nutrient medium.

What has been said of the cultures on ordinary media applies also to the bile media of Conradi and Kayser. The results with these methods show no advantages over the ordinary methods. My own results indicate a distinct disadvantage. I found no evidence that bile uniformly augments the growth of the bacilli. The experiments which Meyerstein[12] recently performed proved that the bile salts do not possess any "anreicherung" influence upon the growth of the typhoid bacilli. His observations, as well as those of Nicolle and Adil-Bey[13] and those of Levy[14], show moreover that these salts exert a detrimental influence upon the growth of other organisms. In conditions, therefore, which simulate typhoid fever and in which other organisms than the typhoid bacillus may be present in the blood, our knowledge of the inhibitory influence of bile on certain bacteria (for instance, the pneumococcus) makes it evident that a negative result might

be obtained whereas the use of the ordinary media might have resulted in a positive finding, and, as we have seen, the ordinary media will also not interfere with the development of the typhoid bacillus.

I wish to draw particular attention to the use of 2 per cent. glucose agar.[7] This medium not only permits good growth of the typhoid bacillus and other organisms,* but the colonies of the typhoid bacillus develop in it in a characteristic way. The features of the colonies on the medium are as follows: They usually appear in the first twenty-four to thirty-six hours of incubation, and are pin-point in size with a disproportionately wide area of green coloration around them. This areola is well defined at the circumference and may be limited by a ring of darkened blood. The colonies show little tendency to increase in size for the first two or three days, whereas the surrounding green areola widens very rapidly. This description applies only to colonies of typhoid bacilli in the depths of the medium. The surface colonies also develop a green color, but they are much larger than the deep colonies and present nothing that may be considered characteristic.

The development of a green coloration about the colonies in the glucose blood medium is a feature that is not restricted to the typhoid bacillus itself; other bacteria may give rise to the same phenomenon. Ruediger[15] studied the question of the production of this pigmentation and found that the pneumococcus, the streptococcus, the Staphylococcus aureus, and the typhoid bacillus produce it; whereas B. coli does not, producing instead a rapid and diffuse hemolysis. From our experience, however, the only colonies that need to be considered from a differential standpoint are those of the Staphylococcus aureus, the B. coli, and the paracolon group. The Staphylococcus aureus grows usually in much larger and more disc-like colonies; and in addition to the green color which it produces, there develops within twenty-four to thirty-six

*Although this medium is better than the bile media for routine work, in connection with other bacteria than typhoid bacillus, it is sometimes not so good as agar unless serum be added.

hours, a clear area (complete hemolysis) immediately around the colonies between them and the area of green coloration. This hemolytic ring may be very narrow and in the early stages of incubation may be entirely absent.

In one case of general infection by the colon bacillus, which we had the opportunity of studying, the colonies in the glucose medium developed to a much larger size within the given period than do colonies of typhoid bacillus. They showed, moreover, a greater tendency to break through and spread out upon the surface of the medium, and produced gas. Gas bubbles were also produced by the paracolon bacillus; but the colonies otherwise resembled very closely those of typhoid bacillus.

When, therefore, we find that stained smears from the colonies of the type described as characteristic for the typhoid bacillus show the presence of a Gram negative bacillus, we can safely place the organism in the typhoid-colon group.* Moreover, when colonies are present on the media, which do not correspond to the type described, the presence of the typhoid bacillus may be excluded. The character of the colony which the typhoid bacillus produces on 2 per cent. glucose blood agar affords us, then, a great help in identifying the organism early. Most of our positive results on the glucose agar were obtained within twenty-four hours after taking the culture. In some instances the typical typhoid colony developed within sixteen hours. Delay in development of the colonies may at times be accounted for by errors in the titer of the medium.

Of the one hundred and fifty-four cultures taken promiscuously, some for diagnosis and others for research, one hundred and ten gave growths of typhoid bacillus and two of paracolon (so-called paratyphoid) bacilli. In one case of typhoid fever complicated by pneumonia and otitis media, a streptococcus was obtained from the blood. The typhoid bacillus was no longer present (the Widal reaction was positive). In another

*All the bacilli isolated in our cases were, of course, further identified by the study of their cultural features and by the presence of agglutination with immune typhoid serum.

case, studied through the kindness of Dr. Eli Moschcowitz, both the typhoid bacillus and a streptococcus were found in the same culture. The results obtained with 2 per cent. glucose bouillon, 2 per cent. glucose agar, and ammonium oxalate solution were the most encouraging; so that our experience leads us to suggest the use of these three media for diagnostic work.

As for the quantity of blood, it may be said that 2 c.c. are sufficient to give positive results in 80 to 85 per cent. of positive cases; but where a larger amount of blood can be withdrawn without inconvenience, it is desirable to obtain it, especially in the later weeks of the disease when the organisms are apt to be very few in number. It is necessary to draw attention to the fact that while the total percentage of our positive results is about the same as that given by other authors, most of our cases were studied during the third and fourth week, and as the results are generally considered to be better in the first and second week, the methods which we have decided to adopt for routine work seem to promise better results than the methods generally used.

SUMMARY No. VI.

Week of Disease	Number of Cultures	Cultures positive	Widal positive
1	8	7—88.5%	2—28.5%
2	44	39—88.6%	28—63.5%
3	42	25—60%	36—86%
4	15	8—53.33%	12—80%
5	7	5—71.5%	5—71.5%
6	3	1—33.33%	3—100%
7	3	1—33.33%	2—66.66%
Totals	122	86—71%	88—72.8%

SUMMARY No. VII.

Relapses.

Intercurrent relapses, 5—all positive		
Day of relapse	Number of cases	Result of culture positive
2	5	3
3	5	4
4	2	1
5	4	4
6	2	2
7	2	1
11	1	1
12	1	0
14	1	0

The last two summaries permit us to draw certain deductions concerning the efficiency of the blood culture as a diagnostic means in that stage of the disease when other means are unavailing. They also draw our attention to the investigation of the relationship of the bacteriemia to the course of the disease. As shown in Summary No. VI, and as already mentioned above, the results obtained agree in general with those of other investigators. The relationship of the positive blood culture and the positive Widal reaction has been studied by a number of authors. The statistics of Coleman and Buxton[16] show that many of the positive cultures antedate the presence of the Widal reaction. Ghaetghens' studies showed that of 917 Widal tests made, in the first week of the disease 25 per cent. were negative, in the second 10 per cent., and in the third 4.7 per cent. He also found that in 140 cases in which the Widal reaction remained negative, 34 were diagnosed by positive blood cultures, an experience previously shared by a number of other observers. Our own results confirm the previous observations.

The lack of relationship between the result of the culture and the type and severity of the disease has also been noted by nearly

all the writers who have reported on large series of cases. Though some fever is usually present at the time when the blood culture is positive, there is no direct dependence of the result upon the height of the temperature. A positive result may be obtained with the temperature at 100° F. as frequently as at 105° or 106°, provided such a temperature occurs in the course of the active stage of the disease. A number of our cases yielded positive results shortly before defervescence, that is, within one, two, or three days; but in no case was a positive result obtained after defervescence was established. Conradi's results in afebrile cases of the disease are certainly exceptional. Coleman and Buxton state that in cases with a long duration, the bacillus is in the blood as long as the temperature persists. My own results support this view in part only. We must distinguish in prolonged cases between those in which the prolongation is due to the disease itself, and those in which prolongation is due to some complication (such as phlebitis or bronchopneumonia, etc.). In the former group of prolonged cases, positive results may be expected. The cases with intercurrent relapses may be regarded in the same group as the last mentioned. The five cultures of our series which were taken in such cases were all positive (see Summary No. VII).

We have had the opportunity of studying twenty-three relapses, sixteen of these gave positive results, approximately 70 per cent., a figure which is nearly the same as that given by a study of the primary attacks. Our experience with negative cultures during the afebrile period warrants the conclusion that in the relapse we are dealing, not with the continuation of the original bacteriemia, but with a new bacteriemia. In the intercurrent relapse it is possible that the bacteriemia is continuous with the original bacteriemia. In four of the sixteen cases of relapse with positive results, negative results were obtained in the primary attack. An analysis of the results obtained on different days of relapse shows (although the series is too small as yet to be conclusive) that the results are better when the fever nears the fastigium than they are in the earlier days. In one case we had the

opportunity of making cultures on the third, seventh, and eleventh days of a relapse. The first two cultures were negative and the third positive. This observation also confirms the view expressed by Schottmüller, that in the true relapse there is a new invasion of the blood.

From a consideration of the results obtained by most investigators it appears to be certain that the bacteremia is concerned in the production of at least some of the clinical aspects of the disease. As Coleman and Buxton state, the number of positive cultures is such that one must conclude that the typhoid bacillus is present in the blood in every case of typhoid fever at some time or other. My own studies with the different media indicate that negative results in the early stages of the disease are accidental. These observations are important, not only from the standpoint of etiological and pathological studies, but also from the standpoint of diagnosis, for they show that a continued fever (and this conclusion was drawn by Schottmüller, and later by Libman[18]) which lasts for several days after the cultures have shown the blood to be free from typhoid bacilli is in all probability not a case of typhoid fever.

To sum up: all the results hitherto obtained show that in typhoid fever there is a bacteriemia which becomes progressively less marked as the disease goes on. Whether the cases which extend beyond the third, fourth and fifth weeks, and in which positive results are obtained, are due to repeated invasions of the blood current or not, is a question which can not, at present, be decided. From the present state of our knowledge it is difficult to formulate a definite view of the significance of the bacteriemia in typhoid fever. The case recently published by Conradi[19] in which bacilli were present in the blood before the onset of the fever, and the case described by Widal in which a positive blood culture was obtained on the second day of the disease, would appear to lend strength to the view of Schottmüller concerning the close relation of the bacillemia to the fever. Certain facts presented by our own studies make us hesitant concerning the occurrence of bacillemia from the very inception of the disease.

for in one case the culture taken on the fifth day was negative, and another culture taken a few days later was positive. In the second case, two cultures taken during a relapse were negative, and the third positive. We are in need of some studies of cases in which the blood cultures were made on the first or second day of the disease (or the relapse).

Our studies do not warrant us in drawing any conclusions concerning the relation of the number of bacilli present to the prognosis of a given case. Schottmüller and Schüffner are of the belief that there is a relationship. Further studies in this direction are also desirable. It is not at all unlikely that the study of the biological differences of the organisms from the blood of different patients will throw some light concerning both prognosis and therapy.

Our studies permit us to draw the following conclusions:

1. The bactericidal influence of the blood in typhoid fever in relation to the obtaining of positive results in the blood cultures has been overestimated. Great dilutions of the blood are not essential; a number of media will give good results.

2. The best results in our experience were obtained with the use of 2 per cent. glucose bouillon, 2 per cent. glucose agar, and ammonium oxalate solution.

3. On 2 per cent. glucose agar the typhoid bacillus grows in such a characteristic way that the presence of a certain type of colony on it is quite disagnostic and the absence of such a colony points very strongly against the presence of the typhoid bacillus.

4. The bile media were not found to be as reliable as the media mentioned above.

5. The results presented are in agreement with those obtained by others. The total positive results obtained by us are in agreement with the results obtained by others notwithstanding the fact that more of our cases were studied later in the course of the disease.

6. Although the maximum results are obtained in the first and second week there is not sufficient proof as yet that the bacilli are present in the blood from the very inception of the fever.

7. Protracted cases yield positive results if the continuation of the fever is not due to complications (or starvation).

8. A continued fever lasting several days after the blood has been shown to be free from typhoid bacilli will nearly always prove not to be a case of fever.

9. The results in relapses are the same as those in the primary attacks. The bacillemia in the relapses is due to a new invasion.

10. We can not draw any definite conclusions, as yet, concerning the value of the blood cultures in determining the prognosis.

It is with a deep sense of gratitude that I wish to acknowledge my indebtedness to Dr. E. Libman for his advice and constant guidance in this work. To Drs. Hertz, Ryttenburg and Fried, I wish to express my thanks for their kind assistance.

References.

1 Castellani. *Settimana Medica,* 1899.
2 Schottmüller. *Münch. med. Woch.,* 1902, No. 38.
3 Lemiere. *Ibid.,* 1906, No. 32.
4 Eppenstein and Korte. *Ibid.,* 1906, No. 24.
5 Müller and Graef. *Centralbl. f. Bakt.,* xliii, 1907.
6 Klodnitzky. *Russki Vratch.,* vol. VI, Nos. 27, 28, 29.
7 Libman. *Johns Hopkins Hosp. Bull.,* 1906, July.
8 Epstein. *Amer. Jour. Med. Sciences,* 1907, Sept.
9 Conradi. *Münch. med. Woch.,* 1906, No. 34.
10 Kayser. *Ibid.,* 1906, No. 17.
11 Schüffner. *Ibid.,* 1907, No. 35.
12 Meyerstein. *Centralbl. f. Bakt.,* xliv, 1907.
13 Nicolle et Adil-Bey. *Ann. de l'institut Pasteur,* 1907, No. 1.
14 Levy. *Virchows Arch.,* 1907, Feb.
15 Ruediger. *Jour. Infectious Dis.,* 1907, Sept.
16 Coleman and Buxton. *Amer. Jour. Med. Sciences,* 1907, June.
17 Ghaetghens. *Arb. a. d. Kais. Gesundheitsamte,* 1907, H. 1
18 Libman. *Trans. N. Y. Academy of Medicine,* 1907, Mar. 7.
19 Conradi. *Münch. med. Woch.,* 1907, No. 41.

Discussion.

Dr. Thomas Flournoy asked as to the details of the dilution of the blood by the media.

Dr. Epstein said that he had used 100 to 120 c.c. of plain bouillon and 2 per cent. glucose bouillon, and to that quantity he had added about 2 c.c. of blood.

Dr. Charles Norris said that he thought Dr. Epstein's paper very admirable and sane. He was pleased that Dr. Epstein had found that the bile salt method was not so good as it was at first considered. He had always thought it a comparatively easy thing to get growth on any bouillon in a few days. An important point was never to throw away a blood flask before five or six days. Not infrequently clouding of the broth did not appear until the third or fourth day.

Dr. E. Libman wished to emphasize two or three points. In the first place, there was the necessity for studying a large number of cases carefully in order to see whether the point made by Dr. Epstein would be confirmed; that is, that if the temperature remain nearly constant for several days after a negative blood culture, typhoid fever could be excluded. Several cases recently seen tended to confirm this statement. There was also a necessity for full studies on the bacteriemia in the first few days of the disease. Upon the results of such studies would depend greatly our conception of the etiology of typhoid fever. Personally, he thought one could not yet be sure of the conclusion that the bacillemia is the cause of the lesions. It was still undecided whether the lesions in the intestine caused the bacillemia or the bacillemia caused the intestinal lesions.

A NEW METHOD FOR THE QUANTITATIVE DETERMINATION OF ACETONE IN THE URINE.

T. STUART HART, M.D.

(From the Laboratory of Dr. E. G. Janeway.)

Although a number of methods have been devised for the quantitative estimation of acetone in the urine, at the present time the method of Messinger,[1] as modified by Huppert,[2] is the one most frequently employed, and is usually regarded as the most accurate one at our command.[3]

A recent paper by Folin[4] offers the first satisfactory method for separately determining the acetone and diacetic acid of the urine. By this method, acetone and diacetic acid are estimated by the Messinger-Huppert method; acetone is separately estimated by drawing it into a suitable absorbing solution by means of a current of air. From these data the diacetic acid may be calculated by subtracting the amount of acetone obtained by means of the air current, from the acetone determined by the Messinger-Huppert method. Folin has shown that under the conditions of his method practically all of the acetone in 20 c.c. of urine is by a continuous current of air, in twenty-five minutes, transferred to the absorbing cylinder, and may there be rapidly estimated by titration. In a preceding paper, I have shown that my experiments following those of Folin corroborate the correctness of his statements.

While working with Folin's method, the thought occurred to me that if we could convert diacetic acid into acetone, both could be transferred by a current of air to the absorbing bottle, and we could thus obtain a short method for the estimation of acetone and diacetic acid in the terms of acetone. The conversion of diacetic acid into acetone and carbonic acid is readily accomplished by heating to the boiling point. The determination is conducted in the following manner:

The apparatus used is a slight modification of one devised by Folin for the estimation of ammonia.[5]

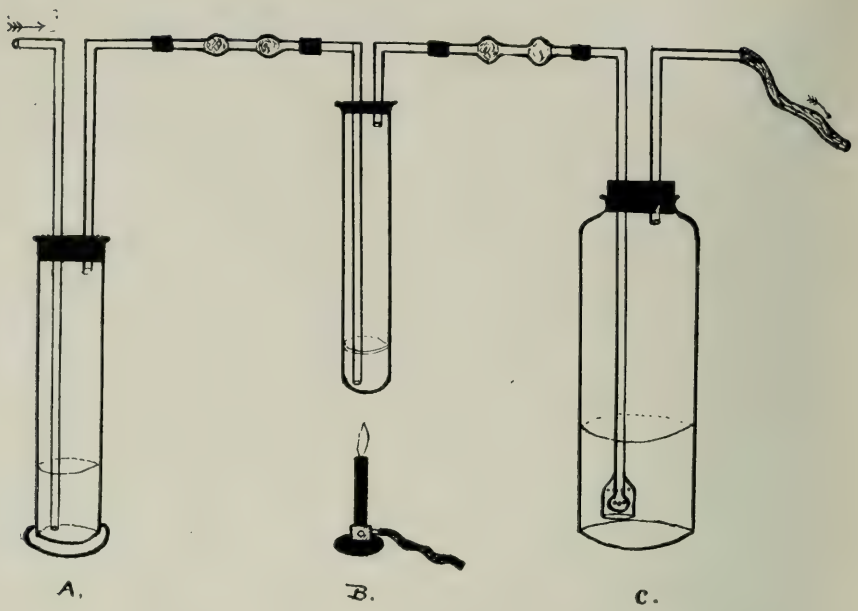

Diagram.

A is an aerometer cylinder.

B is a large test tube, two inches in diameter, raised so that it can be easily heated.

C is a wide-mouthed bottle fitted with a Folin tube.[6] The connections between the cylinders are made with bulk tubes containing cotton.

A contains alkaline hypoiodite to absorb any acetone which may be present in the laboratory air.

B contains 20 c.c. of the urine to be examined, 10 drops of a 10 per cent. solution of phosphoric acid, 10 grams of sodium chloride, and a little petroleum.

C contains 200 c.c. of distilled water, an excess of decinormal solution of iodin (carefully measured), and an excess of 40 per cent. solution of sodium hydrate.

The apparatus is then connected with a Chapman pump and a steady current of air is drawn through at a moderate rate for twenty-five minutes. During this period, a lamp is placed under the tube containing the urine and the contents brought just to a

boil; this is done twice, allowing an intermediate period of about five minutes.

By the application of heat the diacetic acid is converted into acetone, and at the end of twenty-five minutes will have been drawn into the absorbing bottle and have been converted into iodoform.

The contents of the absorbing bottle (C) are now acidulated with strong hydrochloric acid, when if iodin be present in excess a brown color will develop. This is now titrated with a decinormal solution of sodium thiosulphate, using starch as an indicator as in the Messinger-Huppert method. The amount of iodin used in the formation of iodoform is calculated by subtracting the quantity of thiosulphate solution used from the quantity of decinormal iodin solution placed in the absorbing bottle. One c.c. of the iodin solution is equivalent to 0.976 mgms. of acetone.

The following are a few results obtained in diabetic urines, with comparative findings by the Messinger-Huppert method:

No.	Date 1908	Messinger-Huppert Method. Grams per liter	Author's Method. Grams per liter	Difference Grams per liter.	Difference Per cent.
1	Jan. 9	1.430	1.440	+0.010	+0.7
2	" 11	0.766	0.703	—0.063	—8.2
3	" 13	0.878	0.888	+0.010	+1.1
4	" 14	1.425	1.469	+0.044	+3.1
5	" 14	0.629	0.570	—0.059	—9.3

In experiments 1, 2 and 5, after twenty-five minutes of air current and heat by the described method, a trace of acetone was found in the tube containing the urine; at times the air current was probably a little too slow in these determinations.

In three of the above determinations, the estimation was a little high, and in two the estimation was considerably too low as compared with the Messinger-Huppert method. The low determinations may be explained by the fact that the air current

was too slow, as in each a trace of acetone could be detected in the original urine after the air current had passed for twenty-five minutes. The investigations of Schwartz[7] show that he was able to recover 96 to 97 per cent. of the acetone of the urine by the Messinger-Huppert method.

This method may be used in conjunction with Folin's method to estimate the relative amounts of acetone and diacetic acid in the urine. The apparatus and solutions are prepared as described above and an air current drawn through the urine for twenty-five minutes without the application of heat. By this means, as suggested by Folin, all the acetone is drawn into the absorbing bottle and may be estimated by titration. A fresh alkaline hypoiodite solution is then placed in the absorbing bottle; heat is applied to the urine tube to convert the diacetic acid into acetone; and this is drawn off by an air current for twenty-five minutes as above described, and is in turn estimated by titration.

The following table shows a few results obtained by this method, and a comparison of these with the results obtained by the Messinger-Huppert method.

		Aceton in grams per liter.					
		I	II	III	IV	V	
No.	Date 1908	Air Current 25 mins.	Following I Air Current and heat 25 mins.	Total I and II	Messinger-Huppert Method	Differ. III and IV	Differ. Per cent
1	Jan. 27	0.142	0.390	0.532	0 561	—0.029	—5.4
2	" 28	0 234	0.781	1.015	1 056	—0.041	—3.4
3	" 30	0.098	0.561	0.659	0.675	—0.016	—2.4
4	Feb. 4	0.132	0.473	1.605	0.625	—0.020	—3.2

Note:—No. 1. Air current was very slow; at the end of the determination acetone could be detected in the urine.

Nos. 2 and 3. No acetone could be detected at the end of the determinations.

No. 4. A trace of acetone detected after determination.

The method as proposed affords values approximating very closely to those of the Messinger-Huppert procedure, while the time required for a determination is only half an hour as against two to two and one-half hours demanded by the Messinger-Huppert process.

Note:—To obtain a rough idea of the amount of decinormal iodine solution needed in the absorbing bottle, mix in a test tube 10 c. c. of the urine to be examined and 1 c. c. of a 100 per cent. solution of ferric chloride. Allow this to stand for two minutes and compare the color thus developed with the color of 100 per cent. ferric chloride solution in a test tube of equal size. If the color of the two test tubes be approximately of the same depth, 10 c. c. decinormal iodine solution will be sufficient to combine with the acetone set free from 20 c. c. of urine. If the color of the urine mixture be darker than that of the ferric chloride solution, dilute the urine mixture with distilled water until its color approximates in depth the color of the ferric chloride solution. The amount of decinormal iodine needed can then be roughly estimated as follows:

Urine	Fe_2Cl_6 (100% sol.)	H_2O	
10 c.c.	+ 1 c.c.		= needed 10 c.c. decinormal iodine sol.
10 c.c.	+ 1 c.c.	+ 10 c.c.	= needed 20 c.c. decinormal iodine sol.
10 c.c.	+ 1 c.c.	+ 20 c.c.	= needed 35 c.c. decinormal iodine sol.
10 c.c.	+ 1 c.c.	+ 30 c.c.	= needed 50 c.c. decinormal iodine sol.

References.

1 Messinger. *Ber. d. chem. Ges.*, 21, 1888.
2 Huppert. *Anal. des Harns*, 1898.
3 Waldvogel. *Die Acetonkörper*, 1903, p. 14.
4 Folin. *Jour. of Biol. Chem.*, III, 1907, p. 177.
5 Folin. *Zeit. f. physiol. Chemie*, XXXVII, 1902, p. 161.
6 Folin. *Jour. of Biol. Chem.*, III, 1907, p. 182.
7 Schwarz. *Arch. f. exp. Path. u. Pharm.*, XL, 1898.

Discussion.

Dr. A. Mayer said that he thought this was the best method for the determination of acetone and diacetic acid that he knew of. Shortly before the publication of Folin's paper, Embden, of Frankfort, studied this question and read the results of his studies before the Kongress für innere Medizin of 1907. His method somewhat resembled this, but differed in that Embden distils the acetone from the urine, using a temperature of only 35° C. He found that was sufficient to distil over the entire acetone in the urine. He then raised the urine to boiling point, converting the diacetic acid into acetone, and in that way got two quantities, the first representing the free acetone in the urine, and the second, the acetone derived from diacetic acid. Dr. Mayer thought Dr. Hart's method superior to this, because a temperature of 35° C. was exceedingly difficult to regulate; and a temperature running higher would certainly convert the diacetic acid into acetone. The simplicity of the method was greatly in its favor. Whether the ammonia which is contained in all these urines might have some influence in the determination of the acetone, was a question which should be studied. All of the diabetic urines containing large quantities of acetone and diacetic acid also contain large quantities of ammonia, and ammonia may be drawn over in the same way as the acetone. It was a question whether the ammonia had any influence on the iodin solution.

Dr. Hart regretted that he was not familiar with Embden's work on this subject. Other attempts had been made on these lines, which had not been successful in some details. Strauss attempted something in the same line, but apparently used too large quantities of urine, since it was necessary for him to continue the procedure for twenty hours. As regarded the ammonia, Dr. Hart thought that the phosphoric acid added to the urine would hold back the ammonia by neutralizing it; so that the error was not very considerable.

PRIMARY TUBERCULOSIS OF THE MESENTERIC GLANDS: REPORT OF INFECTIONS WITH BACILLI OF THE HUMAN TYPE.

BY ALFRED F. HESS, M.D.

Before reporting the cases which form the subject of this paper, it may be both profitable and interesting to bring together all other instances in which tubercle bacilli have been found, cultivated, and differentiated in mesenteric glands, in order to see whether we are justified in drawing any general conclusions. I shall not consider the question of the frequency with which primary mesenteric tuberculosis is encountered. This is a subject concerning which inexplicable differences of opinion still exist, as is indicated by a comparison of the English statistics, which show a primary lesion of the intestine and its glands 290 times among 1,560 autopsies of children, that is to say, in 18.6 per cent., with those of 369 cases of tuberculosis coming to autopsy in New York and its environs, among which only five were of intestinal origin, a little more than 1.3 per cent.[1]

Leaving this question open, let us turn to those cases in which the type of infecting organism has been isolated and studied. On reviewing the literature I have been able to find seventy-one instances where this procedure has been followed. This list may not include all, but it certainly comprises the great majority of cases, and is sufficient for a trustworthy analysis.

Eighteen cultures were studied by the British Tuberculosis Commission, twenty-seven by the German Commission, and twenty-six by other investigators. A cursory review of these cases, best seen when they are arranged in tabular form (Table I) brings to light the fact that the majority are instances of infection with the bovine type of bacillus; in fact, forty-four of the seventy-one, or 62 per cent., are of this nature. These figures are not conclusive in the decision of the question as to the relative importance of bovine and human infection in general, for they consider only one group of cases, and, as I have said elsewhere,[2] only a consideration of a large number of unselected cases of

TABLE I.

A Summary of Reported Cases of Primary Mesenteric Tuberculosis.

	Human		Bovine	
	Children	Adults	Children	Adults
British Tuberculosis Commission	8	....	10	....
German Tuberculosis Commission*	7	5	15	....
Smith ..... *Trans. Ass'n American Physicians.*	1	....	1	....
Smith ..... *Amer. Jour. Med. Sciences, 1904*	1	2	....	....
Smith and Brown.... ..... *Jour. of Med. Research, Sept. 1907*	....	1	1	....
Ravenel ..... *Univ. Penn. Med. Bull., 1902*	...	....	1	....
DeSchweinitz, Dorset and Schroeder *Bureau Animal Ind., Bull. 52,* ii, '05	....	....	2	....
Fibiger and Jensen° ..... *Berl. klin. Woch., 1902, 1904, 1907*	1	1	5	....
Damann and Müssemeier ..... *Untersuch. d. Tb. der Mens. u. Tiere, 1905*	....	....	....	1
Hoelzinger ... . *Inaug. Diss. Giessen, 1907*	....	....	....	1
L. Rabinowitz ..... *Arb. a. d. Path. Inst., Berlin, 1906*	....	....	2	1
Westenhoefer .... *Berl. klin. Woch., 1903*	....	....	1	...
Eber .... *Beit. z. Klinik d. Tuberkulose, 1905*	....	....	2	....
Fife and Ravenel ..... *Proc. Phila. Path. Society. 1905*	....	...	1	....
Totals.....	18	9	41	3

* In one case not included in the Table, both types were isolated from the mesenteric glands. In two cases in the Table, a bacillus of different type was found elsewhere than in the mesenteric glands.

° Including cases 4, 5, 6, 7, 8, 11 and 12 of authors.

pulmonary, intestinal, glandular, bone and other infections, can finally throw light upon the relative incidence and importance of these two groups of tuberculosis. As yet we have no data based upon such a series of cases. Both Commissions have selected too many instances of abdominal tuberculosis to make their results of value from this point of view. The significance of their investigations lies in other directions. However, the fact that 62 per cent. of intestinal or mesenteric gland tuberculosis proved to be of bovine origin is worthy of note. It means that the tubercle bacillus of cattle is a factor that can not be disregarded, as Koch maintains, in its pathogenicity to man. Again, when this 62 per cent. is compared to the percentage of bovine infection which has been demonstrated in other organs of the body, it emphasizes the fact that the mesenteric glands form the chief portal of entry for the bovine bacillus, with the tonsils alone to share this distinction.

The next point which compels notice is that of these seventy-one cases only twelve occurred in adults. The significance of these figures is somewhat dimmed by the fact that the glands of children were especially selected for the investigations. Nevertheless, although this may not be the correct ratio, all autopsy records show the marked preponderance of mesenteric gland tuberculosis in children as compared to adults. The statistics are absolutely sufficient, however, if we consider children and adults separately in two distinct groups and compare the proportion of human and bovine infection in each. Such a comparison reveals that of the fifty-nine cases in children, forty-one were bovine infections, some showing an atypical strain of bacillus; whereas of the twelve adult cases only three were of bovine origin. This difference in the type of infection can not be due solely to increased exposure on the part of young children to food contaminated with bovine bacilli, such as infected milk, for adults in the course of many years must be similarly exposed. We must attribute this difference either to a diminished natural resistance on the part of the child, in the nature of an increased permeability of the intestine, or to a lack of protective power of

the lymph nodes, or we must concede a degree of acquired immunity towards bovine bacilli on the part of the adult.

When we inquire into the course of the disease produced by the two types of bacilli in mesenteric gland tuberculosis, we find no points of differentiation. In either case the disease is generally progressive. However, instances of limited infections occur in each variety and are encountered generally when the tuberculous lesion is of secondary importance, the cause of death being some other infectious disease. For example, the bovine type has been found in a solitary calcareous node,[3] and again in the ascitic fluid of a patient who recovered and was well three years later.[4]

As regards the character of these lesions, Baumgarten has claimed that the human type of bacillus more commonly causes caseation, whereas the bovine organism incites calcification. Viewed from this standpoint, the seventy-one cases show no distinctions. Caseation was found in all but four instances, and these were of the human variety. Whether calcification develops probably depends more upon the virulence of the bacillus than upon its type, and also upon the peculiarities of its host. For instance, the second interim report of the British Commission shows that calcification was almost universally found in the mesenteric glands of swine, calves, and cows fed with human sputum, which may, I believe, be interpreted in this way. Finally, it should be mentioned that the German Commission reported that in seventeen cases of tuberculosis found at autopsy in children dying of acute infectious diseases, animal inoculation proved negative, in spite of the fact that tubercle bacilli were found in these nodes in eight instances, in some cases in exceptionally large numbers. This emphasizes the limitation of animal inoculation and the necessity of microscopical examination in the diagnosis of tuberculosis. It, furthermore, shows the resistance of children to tuberculous infection, and their ability to arrest the disease by killing the invading bacilli.

The cases which I shall now report, three in number, are all instances of primary mesenteric gland tuberculosis.

Case 1.—A. C. A child three years and nine months old,

admitted to the New York Foundling Asylum for malnutrition. No history was obtained. The autopsy, performed January 23, 1907, by Dr. Howland, who kindly sent me the pathological material, disclosed the following unexpected anatomical conditions: enlargement of the follicles in the lower portions of the small intestine, marked prominence of Peyer's patches, with three or four deep transverse ulcerations, enlargement and caseation of the mesenteric glands, moderate enlargement of the spleen. The lungs were negative; the mediastinal glands slightly enlarged. Pathological diagnosis: Tuberculosis of the intestine and mesenteric glands.

Smears made from the cheesy mesenteric glands showed a few tubercle bacilli. No bacilli were seen in smears from the small, slightly anthracotic bronchial glands. On January 25, two guinea-pigs were inoculated subcutaneously with bits of mesenteric gland, and one with bronchial gland tissue. Twenty-one days later, the pigs inoculated with mesenteric gland tissue were chloroformed, as they showed enlargement of the inguinal glands, although they had both gained slightly in weight. Both were found to be tuberculous. Tissue from the inguinal glands, iliac glands, and spleen was used for culture on dog serum and egg media. The pig inoculated with the bronchial gland was chloroformed after thirty-four days and showed no tuberculosis. Cultures were readily obtained from the spleen and inguinal glands; they grew after twenty-three days on the serum and later on the egg media. They appeared as round colonies at the upper part of the tube where the media was in an extremely thin layer. Later they spread out in heavy membranes. The bacilli were in the form of straight rods from 1.5 to 2 micra in length, and were similar in all the tubes. In subsequent cultures they varied considerably in length and contour. Thus in facility of culture and in morphology they resembled the human type. Intravenous inoculations into rabbits confirmed this opinion. For this purpose, 0.5 c.c. of a suspension of bacilli in salt solution corresponding in density to a twenty-four hour bouillon culture of typhoid bacilli was employed. As the table shows (Table II), the

bacilli possessed but slight virulence towards rabbits, causing only lesions after a period of two and three months. Bovine bacilli when thus inoculated invariably produce a generalized tuberculosis.

Case 2.—P. H. A twenty-two months old infant was admitted to the Babies' Hospital, in the service of Dr. Holt, to whom I am indebted for the following information. The family history showed that the father had suffered from a cough for an indefinite period. The child was nursed for four months and then fed on raw milk mixtures. It had a previous history of pertussis and measles, and had been in the hospital twice before, once suffering from an "acute gastro-intestinal toxemia," the second time from "bronchitis and anemia." It was now admitted on account of diarrhea.

Examination showed the baby prostrated, abdomen lax, and glands not palpable, except those in the inguinal region which were the size of shot. The temperature on admission was 104.3° F., weight 21 lbs. 10 oz. A diagnosis of tuberculous enteritis was made. Delirium soon supervened and was followed by death.

The autopsy, performed on September 3, 1906, by Dr. Martha Wollstein, whom I have to thank for the pathological material, revealed the following conditions: tuberculosis of the intestines and mesenteric lymph nodes, fatty liver, splenic tumor. Lungs and bronchial lymph nodes negative. Cultures of the heart's blood showed no growth. Sections of the spleen, liver, lung, ileum and mesenteric lymph nodes were made. On microscopic examination the liver, lung, and intestine showed no tuberculosis. In the spleen there were many young tubercles. The mesenteric glands showed numerous giant cells with peripherally arranged nuclei, as well as large areas of caseation.

From this autopsy, a piece of liver which appeared normal, bronchial glands of a deep red color and slightly enlarged, but otherwise negative, and a few large cheesy mesenteric glands were sent to me. Bacilli, many of them long and of beaded appearance, were found on the smears from the mesenteric glands. Five guinea-pigs were at once inoculated subcutaneously, one

with liver tissue, two with bronchial, and two with mesenteric gland tissue respectively. Of the five, the only one to develop tuberculosis was one of those inoculated with mesenteric gland. The autopsy of this pig showed nothing requiring mention except marked enlargement of the retrosternal lymph node. This lesion was found in other pigs often when there was but little tuberculous involvement of the lungs or surrounding tissues.

Cultures were made as in the previous case, but owing to a mishap no growth resulted; so that new cultures were made from a pig which had been inoculated on November 8 with some incubated tissue. In twenty-one days, discrete colonies appeared upon one egg and one dog serum tube, and soon became confluent and heavy. The individual bacilli were slightly curved and varied in length from 1.5 to 2.5 micra. Virulence tests made with the second and third generation of bacilli, as shown by the table, proved this strain to be of virulence similar to that isolated in Case 1. The reaction test on glycerin bouillon confirmed the conclusion that we were dealing with a bacillus of the human type. When inoculated, the bouillon was 2.1 per cent. acid to phenolphthalein, and eighty-two days later it was found to be 2 per cent. acid. According to this culture test, devised by Theobald Smith,[3] bovine bacilli when grown upon acid glycerin bouillon tend to bring the media towards the alkaline reaction, whereas in human cultures the reaction curve, although at first "moving toward the neutral point, soon swings back to a greater acidity."

The father of this child is now strong and healthy, and does not cough. As the infant had been fed on raw milk we might have been inclined, judging from the history alone, to consider this a case of bovine infection.

Case 3.—W. M., a boy seventeen years of age, was admitted to the service of Dr. Gilman Thompson at Bellevue Hospital. His family and previous history gave no indication of tuberculosis. At the time of admission to the hospital, he complained of abdominal pain and diarrhea of three months' standing, accompanied by marked loss of weight and strength.

Examination showed the boy's general condition to be poor,

A few râles were heard in the lungs. The abdomen was held rigid and was generally tender; percussion elicited dullness in the flanks, changing with change of position. The diagnosis was chronic pulmonary tuberculosis, tuberculous peritonitis, and tuberculous enteritis. Death followed four days after admission.

The autopsy performed three hours after death by Dr. Norris, who kindly furnished me the material for examination, disclosed the following pathological conditions: primary acute tuberculous hyperplastic enteritis, acute suppurative peritonitis, intestinal flora on smears, perforation of ileum, acute serofibrinous pleuritis, acute parenchymatous nephritis and hepatitis, suppurative sphenoiditis and otitis media, persistent thymus, bronchial lymph nodes slightly anthracotic, otherwise negative, mesenteric nodes enormously enlarged, most of them hyperemic, the largest showing on section yellowish areas of necrosis.

The large mesenteric glands, which were sent to me on April 15, 1907, were not typically tuberculous on macroscopic examination, resembling somewhat sarcomatous glands. A long search revealed a few acid-fast bacilli. Microscopic examination showed caseation in some sections, in others only a marked swelling and proliferation of the endothelial cells lining the perifollicular spaces. As in the other cases, passage through guinea-pigs was used to obtain pure cultures, bits of glandular tissue being inserted into subcutaneous pockets in the abdominal wall. In this instance both animals died after five days, so that the inoculation of two pigs was repeated with tissue thoroughly washed in salt solution. Both pigs gained in weight, but showed marked enlargement of the inguinal glands. They were chloroformed on May 5, 1907, twenty-three days after inoculation. Cultures were obtained from the inguinal and iliac glands. The growths were profuse and glistening and were successfully transferred to glycerin bouillon. The bacilli resembled those isolated in Case 1, and were mainly straight rods, 1.5 to 2. micra in length, a few being longer. A suspension inoculated into the ear veins of two rabbits proved this strain to have a low virulence.

TABLE II.

Data of Inoculation of Rabbits with Pure Cultures of Tubercle Bacilli.

	Total Age of Culture	Number of Trans.	Age of Culture	Amount Inoculated	Number of Rabbit	Date and Method of Inoculation	Result	Remarks
Foundling Asylum	44 days	2	11 days	0.5 c.c.	250	3-31-'07 Ear vein	Chloroformed, June 9 (2 mos 9 days)	A few foci in kidneys and anterior part of lungs
	44 days	2	11 days	0 5 c.c.	217	3-31-'07 Ear vein	Chloroformed, July 6 (3 mos. 6 days)	Foci in kidneys
Babies' Hospital	37 days	2	10 days	0.5 c.c.	213	1-12-'07 Ear vein	Chloroformed, Feb. 6 (2 mos. 20 days)	Extensive tuberculosis of lungs
	37 days	2	10 days	0.5 c.c.	207	1-12-'07 Ear vein	Chloroformed, Feb. 17 (3 mos.)	A few foci in lungs and kidneys
	53 days	3	12 days	0.5 c.c.	299	1-10-'07 Ear vein	Chloroformed, Apr. 18 (3 mos. 2 days)	Tuberculosis of iris. Foci in kidneys and lungs
Bellevue Hospital	27 days	1	27 days	0.5 c.c.	208	6-5-'07 Ear vein	Chloroformed, Aug. 5 (2 mos.)	Two foci in lungs; a few in kidneys
	27 days	1	27 days	0.5 c.c.	209	6 5-'07 Ear vein	Chloroformed, Aug. 5 (2 mos.)	Large foci in kidneys

Summary.

A review of cases of primary mesenteric gland tuberculosis in which the type of bacillus has been differentiated shows that over 60 per cent. have been caused by the bovine type of bacillus.

Among children the bovine infections greatly prevailed, whereas in adults, infections with the human variety were in the majority.

No pathological or clinical differentiation of the two forms of tuberculosis is as yet possible.

In children, as well as in adults, bovine or human tuberculosis may become limited and healed, and the bacilli may die.

It is interesting to note in contradistinction to the above statistics that the three cases reported by me were all of the human type.

Bibliography.

1 Ravenel. *Amer. Jour. Med. Sciences,* 1907.
2 Hess. *Archives of Pediatrics,* 1907, June.
3 Rabinowitz. *Berl. klin. Woch.,* 1907, No. 2.
4 Damann and Müssemeier. *Untersuchungen über die Beziehungen zwischen der Tuberkulose der Menschen u. d. Tiere.* Hanover, 1905.
5 Smith. *Jour. Med. Research,* xiii, No. 3.

A CASE OF SYPHILITIC INTERSTITIAL SPLENITIS WITH GENERAL AMYLOID DISEASE; A CASE OF HYPERNEPHROMA WITH EXTENSIVE METASTASES IN THE LUNGS.

H. MARTLAND, M.D.

The first specimen which I have to present is a spleen which shows a rare and, at the same time, a rather typical lesion; namely, a marked cirrhosis of syphilitic origin. The organ was removed from a woman, fifty-four years of age, who died on the

medical service of the City Hospital after having been under observation for about two weeks. On admission to the hospital she stated that she was a domestic and gave as her chief complaint vague stomach trouble.

Physical examination revealed a poorly nourished woman, who appeared markedly anemic. Her teeth were very bad; her tongue was coated, and showed a slight tremor. The heart was slightly enlarged, being beyond the nipple line; a systolic murmur was heard at the apex, and over the aortic area. The second aortic sound was accentuated. The pulse was full and regular. On palpating the abdomen, the liver was felt a hand's breadth below the costal margin, its edge being firm and rounded. There was slight tenderness over the epigastrium. The abdominal veins were prominent. The remainder of the examination was negative. The urine was amber, acid, 1.010. Albumin, and hyalin and granular casts were present.

The blood count showed the following:

Erythrocytes	2,384,000
Hemoglobin	15 per cent.
Color index	0.3
Polymorphonuclears	87 per cent.
Large lymphocytes	4 per cent.
Small lymphocytes	9 per cent.

While in the hospital, the patient's temperature was always about normal. The pulse varied from 68 to 108, usually it was around 90. The respirations were increased only at the time of death. The blood pressure varied from 90 to 130. The chief subjective symptoms were nausea, vomiting and diarrhea. She gradually grew weaker, becoming irrational and incontinent. During the last few days there was a marked diminution in the amount of urine secreted. She died of air hunger (probably anemic in origin).

The clinical diagnosis was: Severe secondary anemia, cause undetermined; cardiac hypertrophy; arteriosclerosis; chronic nephritis.

In regard to her previous history, it is noteworthy that she

had contracted syphilis when thirty years old, and had received very little treatment. Three years later she had an operation on the rectum (probably for stricture). When forty years old she was in the City Hospital with a severe gastritis.

The summary of the autopsy findings is as follows: General amyloid infiltration of the spleen, liver, kidneys, adrenals, mesenteric glands and intestine; syphilitic interstitial splenitis; chronic interstitial nephritis; chronic interstitial myocarditis; pulmonary edema; and smooth atrophy of base of tongue.

The spleen was quite large; it weighed 870 grams and measured 17x12x9 cm. It was oval in shape and presented a notched anterior border. What impressed one at the time of the autopsy was its great firmness; on section it cut with difficulty, the knife encountering firm, cartilaginous masses and areas of calcified tissue near the hilum: the cut section was a light hamred color. The capsule was only moderately thickened, and free from perisplenitis. The splenic substance presented a rather unusual appearance, most marked at the hilum. Here the trabeculæ were enormously thick, being 2, 5 or 10 mm. across; they were a pale bluish white, and had a peculiar hyalin, semitranslucent appearance. These bands divided the spleen into small and large, irregular islands of spleen pulp. The large vessels, when cut transversely, showed thick walls with a glistening appearance. The general color of the spleen pulp was light red; but in places near the trabeculæ a very dark red color was seen. The Malpighian follicles were hardly visible.

On staining with a dilute iodin solution, the surface presented numerous dark mahogany-brown points, most of which represented the regions of the arteries of the Malpighian corpuscles. Sections stained with methyl violet showed a diffuse amyloid infiltration, a rose-red homogeneous substance appearing in and around the arteries of the Malpighian follicles, in the capillaries of the spleen pulp, and in the walls of the cavernous sinuses. The deposition of the amyloid material was rather irregular; although diffuse, it was not massive.

Sections stained with the eosin-hematoxylin and Mallory's

anilin blue methods showed enormously thickened trabeculæ, which were composed of a poorly nourished, not cellular, hyalin connective tissue. The reticulum supporting the spleen pulp was greatly thickened, and there was a great waste in the splenic substance. There was also marked atrophy of the lymphoid mantels, the central artery appearing bare in many places.

In other words, we have to deal here with an extensive cirrhosis of the spleen. If we look for the cause, there can probably be no question that it was of syphilitic origin; in favor of this is the extent and distribution of the lesion, which was most marked around the hilum; the appearance of the tissue itself, the presence of thick isolated bands of connective tissue, similar to those seen in syphilitic cirrhosis of the liver, the affection of the blood vessels, the amyloid degeneration (which in this case must be attributed to syphilis), and the certainty of syphilis as an etiological factor.

The liver showed extensive amyloid infiltration; the liver cells were markedly atrophied, due both to pressure and to an anemia caused by the presence of the amyloid material. The kidneys showed marked interstitial nephritis with extensive amyloid infiltration of the capillaries of the glomeruli and the straight vessels of the cortex and medulla.

The second specimen presented, a large hypernephroma of the right kidney, is interesting because it represents a type of these tumors which is made up of polymorphous cells, part of which bear a close resemblance to those of the medulla, while others are more typical or cortical cells. On the other hand, the metastatic nodules seem to be made up almost entirely of more typical cortical cells.

The patient was a colored man, sixty years of age, who was under observation at the City Hospital for seven weeks. He was admitted complaining of vague rheumatic pains and a slight cough, which he had for some time. On admission, fluid was found in his right chest, and on aspiration 1,000 c. c. of clear serous fluid was obtained. The greater part of his abdomen was occupied by what appeared to be an enlarged liver, the lower edge

being felt almost down to the brim of the pelvis, in the median line, at the navel, and on the left side, to two inches below the costal margin. He also had prominent abdominal veins and varicose veins of the legs. Three days after admission, while going into the bathroom, the patient fell, striking his head and back. Soon after this fall he suddenly developed a severe dyspnea, which did not leave him until the following day. Six weeks after admission, fluid was again found in his right chest, and 2,500 c.c. of a bloody fluid was aspirated. One week later he died from an attack of pulmonary edema. The temperature never rose above 100°; pulse rate was 78 to 90. Blood pressure on admission was 210, but was not taken again. The urine was amber, acid, 1.017, and contained a large amount of albumin, leucocytes, red blood cells, and hyalin and granular casts. The blood count was negative.

Autopsy showed a large encapsulated hypernephroma of the right kidney; hypernephroma of the right adrenal; multiple cortical adenomata of the left adrenal; hematogeneous metastases in both lungs; hemorrhagic pleurisy; smooth atrophy at base of tongue; and stasis in all viscera.

The hypernephroma weighed 3,210 grams, measured 27x19 x14 cm. and was well encapsulated. It was composed of three distinct parts. Near the upper pole and near the median line, was a separate mass, 10x11 cm. in diameter, entirely separated from the surrounding tumor by dense connective tissue. It had the same structure as the large tumor and probably represented a hypernephroma of the right adrenal, since this organ could not be found in its anatomical position. To the outer side of this adrenal tumor, and forming the upper portion of the large tumor, was seen a shell of kidney substance, representing the upper pole and upper half of the lateral margin of the kidney; this was composed almost entirely of kidney cortex. The main tumor mass presented the appearance of an ordinary hypernephroma; it was made up of round or oval masses, varying in size and separated by connective tissue; each mass was divided into smaller areas with a small amount of connective tissue around them.

The various display in colors seen was to be attributed to the extremely fatty, hemorrhagic and necrotic areas commonly found in these tumors. The pelvis of the kidney was comparatively free from tumor growth. The tumor cells had, nevertheless, invaded the renal veins; and in the inferior vena cava, at the insertion of the renal vein, was seen a large thrombus, almost occluding the vena cava. This thrombus was composed entirely of cells resembling those in the zona fasciculata of a normal adrenal. The metastases in the lungs were also composed of tumor cells.

With regard to the tumor itself, we have then to deal with what is commonly called an atypical hypernephroma: that is, one which is made up of cellular elements which appear to be derived from the medulla and partly from the cortex. The cells resembling those of the cortex are large polyhedral cells, containing round or oval, deeply staining nuclei. The cytoplasm (in sections which have been passed through alcohol) shows as a clear vacuole, containing a distinct limiting membrane and a little granular debris. They are situated in alveoli which are formed by naked capillaries. The cells simulating those of the medulla are smaller than the cortical cells; they are polyhedral in shape, with faintly staining nuclei, and a finely granular vacuolated cytoplasm. They are contained in alveoli which are formed by coarse reticulum bearing a structure similar to the reticulum of the normal adrenal. The lungs showed a diffuse hematogenous infiltration of cortical cells, the cell nests springing from the alveolar capillaries and growing into the alveoli.

I wish, also, briefly to call attention to the following conditions observed in the histological study of this tumor. The capsule is composed of dense fibrous tissue with a few scattered elastic fibers. It is not very cellular and contains very few blood vessels. In this capsule, surrounded by the fibrous tissue, are numerous collections of small round cells. These cells are mononuclear, with dark staining nuclei and a very scanty protoplasm. They are very decidedly embryonic in appearance. These cell groups seem to invade the interior of the tumor, where occasionally pictures are observed which may be interpreted as rep-

resenting the transformation of these cells into those resembling the medullary cells. It has been held that such cell groups represent immature and embryonic medullary cells.

The capsule and the large trabeculæ also contain many epithelial lined tubules. These tubules are elongated, having a distinct basement membrane, and are lined with cuboidal epithelium. They look distinctly embryonic and are supposed by some to be remnants of the Wolffian body (as persistent Wolffian tubules have been recognized in adrenal rests). Others think that they are renal rests which have become included in the tumor mass, and have assumed an embryonic appearance from the pressure of the surrounding connective tissue—a condition which does not stand without analogy, since we know that indurations or replacement of parenchyma by a foreign invasion is not infrequently followed by a return to embryonic forms in the essential parts of the parenchyma. This, for instance, is the case in a slowly progressive indurative tuberculosis of the lungs. We have often observed a hyalin matter very similar to hyalin casts in the lumen of these tubules.

As to how far a division of this tumor into portions resembling the various types of the normal adrenal cells may be justifiable, I shall not attempt to discuss here on account of the uncertainty concerning this problem.

THE ACTION OF BILE ON THE PNEUMOCOCCUS, STREPTOCOCCUS, AND STREPTOCOCCUS MUCOSUS.

E. LIBMAN, M.D., AND J. ROSENTHAL, M.D.

(Presented by Dr. Rosenthal.)

Our object this evening is to give a description and a demonstration of the lytic action of bile on the above-named organisms. Our presentation is a part of a study which we have undertaken concerning the identification of these organisms.

Neufeld, in 1900, while working on some problems in immunity found that if 0.1 c.c. of rabbit bile is added to 1 or 2 c.c. of a bouillon culture of pneumococci, lysis occurs, the culture clearing in from ten to fifteen minutes. This result was produced more or less by human bile as well as by the bile of monkeys, guinea-pigs, dogs, cats, oxen, and goats. The phenomenon occurred as well at room temperature as at incubation temperature. Boiling the bile had no effect on the result, but freezing retarded the action. If hanging drops were made it was found that the chains became fewer and shorter, the individual shorter and then indistinct, and in a few minutes no remains of the organism could be seen.

Neufeld further found that "crystallized bile," prepared by precipitating with ether an alcoholic extract of bile, also had this lytic effect. This crystallized product, when free from coloring matter, consisted chiefly of the bile salts, and these, in turn, were found to possess the lytic power over pneumococci and Streptococcus mucosus.

From 1900 to 1907, no further work was done on this subject. In 1907, Levy of Berlin proposed to use Neufeld's observations as the basis for a differential test between pneumococci and streptococci. Neufeld himself had not suggested the diagnostic value of the test. Levy confirmed Neufeld's observations after testing five strains of pneumococcus, six of Streptococcus mucosus, and twenty-four of streptococcus. He used sodium taurochlorate in a 2.5 per cent. solution, and found that it had a bacteriolytic action on pneumococcus and Streptococcus mucosus.

His procedure was as follows: He added a 5 per cent. solution of the salt dissolved in nutrient bouillon to an equal amount of the twenty-four-hour culture of the organism to be tested. As a control, he used an equal amount of the same culture and sterile bouillon. With pneumococcus he obtained complete lysis.

Mandelbaum of Munich followed up Levy's work. He used a 10 per cent. solution of sodium taurochlorate in nutrient bouillon. He tested eight strains of pneumococcus, four strains of Streptococcus mucosus, and fifteen strains of streptococcus. To

the twenty-four-hour bouillon cultures of the above strains he added an equal amount of the 10 per cent. solution of the bile salt. Cultures of pneumococci and of the Streptococcus mucosus cleared up rapidly, while cultures of streptococci remained clouded. He found that although streptococci were not dissolved by this solution, they were injured, so that on transplanting to agar plates no growth was obtained. In hanging drops made from the pneumococcus cultures to which the bile salt had been added, he found a few involution or degenerate forms of the organism. Careful examinations were necessary to find these forms. They were usually found by looking at the periphery of a hanging drop, cutting down the light, and allowing a little Loeffler's methylene blue to run under the cover slip. Remains of the pneumococcus and Streptococcus mucosus could be found after two days. Thus he demonstrated that with the bile salt there was not complete lysis; yet after inoculation on agar plates no growth was obtained.

Mandelbaum also made some experiments with animal bile. He recommends ox-bile as it is easier to get, is inexpensive, and mixes well with the cultures. He used 2 c.c. of bouillon culture and 0.5 c.c. of ox-bile. He found that this had a better action than the bile salt and lytic action was complete. At the end of an hour no traces of the organisms could be demonstrated even after staining.

We considered it advisable to take up this study because for several years we have had a method of classification of the organisms in question based on certain observations made by Dr. Buerger, Dr. Hiss, and one of us (Libman). The authors, with perhaps the exception of Levy, did not state distinctly how they classified their organisms, and we therefore thought it was advisable to see how the bile would act on organisms which we have been classifying as pneumococci and streptococci. We have studied ninety-nine organisms: sixty-eight streptococci, encapsulated and non-encapsulated; nineteen pneumococci; and twelve strains of the Streptococcus mucosus. In every instance in which we have classified organisms as pneumococci and as the Strep-

tococcus mucosus, the organisms were dissolved by bile, and we are, therefore, in a position to confirm strongly the work of the previous writers. The clearing of the cultures of the pneumococci usually occurred within a few minutes; in only one instance did we have to wait twenty minutes. The Streptococcus mucosus cultures usually cleared within a minute. In our work we used ox-bile, adding 1-4 or 2-5 bile to the bouillon cultures. The cultures were made in five bouillons, as follows:

1 Neutral phenolphthalein with 1 per cent. pepton.
2 Neutral phenolphthalein with 2 per cent. pepton.
3 One-half per cent. acid with 1 per cent. pepton.
4 One-half per cent. acid with 2 per cent. pepton.
5 Two per cent. glucose bouillon, 1 per cent. acid.

We used these various bouillons to determine which could give the best growths of pneumococcus because at times certain organisms would hardly grow at all. In previous studies and in those now reported, we found that neutral bouillon gives a better growth than acid bouillon.

The bile was usually added to twenty-four-hour cultures. Hanging drops were made and in only a few instances could the remains of any organisms be seen after a short while. The cultures were then allowed to stand at room temperature for a length of time varying between five and twenty-four hours, and inoculations were made on blood agar, according to the method of Drs. Bernstein and Epstein. From the streptococcus cultures to which bile had been added, we were able in every instance to obtain a growth. We recovered the pneumococcus nine times, and the mucosus three times. Thus it is seen that the lytic action is often not complete.

The fact that Mandelbaum obtained no growths from the streptococcus cultures to which bile had been added, is due to the fact that he did not use an optimum medium like blood medium, but did use agar.

It is important to know that the presence of serum or of glucose interferes with the occurrence of the reaction. Nicolle and Adil-Bey pointed this out. They attempted to explain the

interference of the sugar as being due to the fact that the acids produced by the organisms will precipitate the bile salts and thus prevent lytic action. They also found that the addition of certain salts (particularly magnesium sulphate) augments the lytic effect.

We succeeded in causing lysis in glucose bouillon cultures, twice with strains of streptococcus, and three times with the pneumococcus. For diagnostic work, however, the use of glucose bouillon is distinctly disadvantageous.

From what we have said it is readily seen that we have in the bile test a very valuable method of differentiating pneumococci and streptococci. The Streptococcus mucosus is so readily recognized by its morphology that there is no difficulty in distinguishing it from the pneumococcus in early cultures. Our experience leads us to believe that the presence of the type capsule of the pneumococcus and Streptococcus mucosus, as described by Dr. Buerger, and the solution by means of bile are the best methods to be used in attempting to identify pneumococcus and streytococcus.

The value of the type capsule of the pneumococcus for diagnosis is demonstrated by the fact that in every instance in which the type pneumococcus is present, the organism is promptly dissolved by bile. In a later paper we shall present the results of our studies with inulin, the precipitation test and blood media.

Note:—Since this paper was presented to the Society we have made some experiments with taurocholate of soda and have been able to confirm the statements made by previous authors. This salt is somewhat slower than the bile in producing the lytic effects and is expensive. There is no advantage, as far as we can see, in its use.

Discussion.

Dr. E. Libman said that this study had been taken up for a particular reason. As had previously been pointed out, it was known that pneumococci may in the human body become very much altered and acquire some of the characteristics of the streptococcus. There were no methods at our disposal to distinguish such changed pneumococci from streptococci, and this study was

undertaken to find out whether bile would dissolve pneumococci so changed in the body. It had been found that bile will dissolve pneumococci which have obtained some of these peculiar characteristics. So that it looked at present as though solution by bile was the most reliable method we have now to differentiate these organisms.

ECHINOCOCCUS CYST OF THE LIVER WITH RUPTURE INTO THE DUCTS; CHOLANGITIS; CHOLECYSTITIS; PNEUMOCOCCEMIA.

BY E. LIBMAN, M.D., AND B. CROHN, M.D.

(Presented by Dr. B. Crohn.)

The patient from whom these specimens were obtained was a female, aged thirty-two, who was admitted to the Mt. Sinai Hospital in the service of Dr. Gerster, March 2, 1908. The history was rather difficult to obtain as the patient spoke Hungarian only.

Abstract of History.—This is the patient's third attack of pain. The time of the original attack is not known; the second attack occurred about three months ago. Four days before admission the patient had severe pain in the right hypochondrium. There were vomiting, fever and frequent chills. These symptoms have persisted until the present time. The patient was jaundiced yesterday for the first time. She is in the fourth month of pregnancy.

Examination on Admission.—There is distinct icterus present. The liver extends to a hand's breadth below the free border and is very tender. Just to the right of the umbilicus there is an indefinite mass corresponding apparently to the gall-bladder.

Unfortunately no blood count was made, but the spreads of the blood showed no increase in the number of eosinophiles.

The patient was operated upon by Dr. A. A. Berg on the day of admission. The liver was found enlarged and congested. The gall-bladder was distended, tense, reaching down a few

inches below the liver. The gall-bladder was aspirated and about ten ounces of pus were removed. Cholecystectomy was then performed. No stones were found. The wound was drained.

On the evening of March 2, the patient aborted. On March 3 there was repeated vomiting. The vomiting continued; the pulse became progressively more feeble and the patient died. On admission the temperature was about 102.6°, and remained about the same until it rose to 105° shortly before the patient died.

The autopsy was performed on March 5. The important findings were, in brief, as follows:

There was a general fibrinous peritonitis in the upper part of the abdomen on the right side. The spleen was about one and one-half times normal size; pulp rather congested and soft. There were hemorrhages in the mucosa of the stomach. The most interesting findings were in the liver. In the extreme left part of the left lobe of the liver there was present a suppurative echinococcus cyst about the size of a small orange. Over it there was perihepatitis with fairly firm adhesion to the abdominal wall. An old perforation, admitting a lead pencil was found leading into the gall ducts. All the gall ducts in the liver were distended, contained pus mixed with bile and in some of them cysts were found. In the common bile duct there was found a large cyst. At the papilla there was a plug of mucus. There were no unusual appearances in the part of the liver from which the gall-bladder had been removed. There were present some recent thrombi in some of the larger branches of the portal vein in the liver. In some places the thrombi extended into the smaller vessels.

Bacteriological Examination.—The cultures from the material removed from the gall-bladder during life showed a pure culture of pneumococci. A blood culture was made two days after the operation, 7 c.c. of blood being used. There were thirty-one colonies of the pneumococcus to the cubic centimeter of blood. Pneumococci were also found in the blood in a culture made at the post-mortem examination.

The pus in the cyst of the liver showed pneumococci almost

exclusively, and in the ducts there were found pneumococci and colon bacilli.

The case was therefore one of echinococcus cyst of the liver with perforation into the ducts, suppurating cholangitis and cholecystitis due to pneumococci and resulting general infection. The case is certainly of great interest considering that the clinical picture at the time of admission to the hospital was simply that of cholecystitis. It has been known that cases of hydatid cysts of the liver could give the clinical picture of gall-stones, because of cysts being discharged through the bile ducts. This case is of still greater interest. In it the clinical picture before the last attack was the same as that of gall-stones, the attack being due to passage of cysts through the ducts, but in addition was typically that of cholecystitis, and such was even the post-operative diagnosis. The pus from the gall-bladder contained no hooklets and no scolices, so that it was not possible to suspect the true character of the disease until the time of the post-mortem examination.

The frequency with which rupture of hydatid cysts into the gall-ducts occurs is not definitely known. Rolleston states that if the communication between the cyst and the bile-duct is small, the fluid in the cyst may run quietly away, or on the other hand, the cyst may be infected from the bile duct and suppurate. The characteristic cases are those in which the communication between the cyst and the duct is sufficiently large to allow the daughter cysts to escape and cause colic and jaundice from biliary obstruction. Rolleston believes that the hydatid cyst may irritate the mucous membrane in virtue of toxic bodies developed in the contents of dead cysts and set up a descending cholangitis. But in most cases he believes that the cholangitis is due to bacterial infection, very possibly ascending from the duodenum. The infection may spread into the cyst and cause suppuration. In our case the infection probably occurred in this manner, although one can not definitely exclude a hematogenic infection. Rolleston says that such infections have occurred in the course of typhoid fever, infective endocarditis and the puerperium.

We believe in our case that the pneumococcemia was most likely secondary. In our experience we have not found general infections in cholecystitis except when accompanied by cholangitis. There is therefore no reason why the pneumococcus infection in this case may not have been due to the cholangitis, although, as stated above, a hematogenic source of the infection can not be excluded. If the infection were hematogenic, we would, of course, believe that the infection occurred a long time after the rupture of the cyst into the duct because the opening of the channel leading into the duct was lined by smooth mucous membrane.

In some cases of suppurative hydatid cysts no bacteria were found in the pus. The organisms which have been found (citing from Rolleston) are streptococci, Staphylococcus aureus and citreus, the pneumococcus and Bacterium coli. When pus has a fetid odor, anaerobic bacteria are apt to be present.

THE PATHOLOGY OF THE VESSELS IN CASES OF GANGRENE OF THE LOWER EXTREMITIES DUE TO SO-CALLED ENDARTERITIS OBLITERANS.

Preliminary Communication.

LEO BUERGER, M.D.

The subject which I wish to discuss before you to-night is one which presents points of interest both to the clinician and to the pathologist. It is my purpose to give you a brief account of the pathology of the vessels in that rather unique set of cases of spontaneous gangrene which were first described by von Winiwarter. In 1879, this author published the results of pathological findings in a single case of gangrene of the leg in which he found an obliteration of practically all the arteries by a chronic proliferative process which, in his opinion, was due to a new growth of tissue from the intima. He therefore described the condition under a new name, "endarteritis obliterans."

Patients afflicted with this so-called "endarteritis obliterans" present a very varied complex of clinical symptoms which are so characteristic that the diagnosis of the condition is not difficult. We see these patients not infrequently in New York, particularly in the dispensaries and hospitals that treat the Polish and Russian Jews. In a general way, we may divide the symptoms into those which precede and those which accompany and follow the onset of gangrene. The disease usually occurs in young adults between the ages of twenty and forty; and it is because the gangrenous process may begin at an early age that the names "presenile" and "juvenile" gangrene have been employed. In one class of these patients we find rather characteristic attacks of ischemia. The patients complain of indefinite pain in the foot, in the calf of the leg, or in the toes, and particularly of a sense of numbness or coldness whenever the weather is unfavorable. Upon examination we find one or both feet markedly blanched, almost cadaveric in appearance, cold to the touch, with no pulsation in either the dorsalis pedis or posterior tibial arteries. When the feet become warm some color gradually returns. Another set of patients complain particularly of rheumatic pains referred mostly to the leg; others are able to walk but a short distance, for the advent of paroxysmal, shooting, cramp-like pains in the calf of the leg makes it imperative for them to stop short in their walk. Some of these cases give the typical symptoms of intermittent claudication. At times the first evidence of disturbance in an extremity is the appearance of a blister, a hemorrhagic bleb of an ulcer, near the tip of one of the toes, or under a nail, more rarely near the heel; and when this condition ensues, local pain becomes a prominent symptom. When trophic disturbances, such as bleb or ulcer, have once developed, we frequently find that the skin in the neighborhood becomes gangrenous and at this stage amputation is usually imperative because of the intensity of the pain and the progression of the gangrene. Many patients present a condition which simulates that described by Weir Mitchell under the name of "erythromelalgia." When the limb is held in a dependent position, the tips of the

toes become bright red, this color rapidly extending upward over the dorsum of the foot, sometimes only to the tarsus, sometimes to the ankle, or, rarely, even higher up. When the disease involves both extremities almost simultaneously, then the trophic disturbances, the ischemia, or the reddening, give rise to a symptom complex which is often diagnosed as Raynaud's disease. In short, after longer or shorter periods characterized by pain, coldness of the feet, numbness, ischemia, intermittent claudication, and erythromelalgic symptoms, evidences of trophic disturbance appear finally to pass over into a condition of dry gangrene.

Historical.

Although the literature bearing upon the pathology of the disease just described is large, I wish to call attention to some of the more important contributions only. Von Winiwarter and Friedlander ascribed the closure of the vessels to a proliferation of the cellular and fibrous elements in the intima and therefore proposed to call the lesion by the name "endarteritis obliterans." This theory has been accepted by most authors, and even to-day it is to be found in all the text books. Somewhat later, Wilonski pronounced the opinion that the essential change in the vessel walls was due to a multiplication of the elastic fibers, and proposed the name "arteritis elastica" for the condition. Perhaps the most important contributions are those of Weiss and Zoege von Manteuffel, because these authors placed an entirely new interpretation upon the pathological findings. Basing his paper upon the studies of his assistant Weiss, von Manteuffel suggests that the extensive occlusion of the vessels in this disease is dependent upon a primary arterio-sclerosis; that the obliterative process commences in the popliteal artery where it owes its inception to the formation of a parietal white thrombus; and that, by virtue of a gradual extension of the parietal thrombi downward followed by organization, a picture resembling an obliterative endarteritis is produced. In his cases the veins do not seem to be involved in the process. Von Manteuffel comes to the con-

clusion that the thrombosis is due to desquamation of endothelial cells, and that this occurs where the intima shows the most advanced lesions of arteriosclerosis, namely, somewhere in the popliteal artery. In spite of the views expressed by these latter authors, Sternberg, from the study of eight cases, is in accord with the old conception first suggested by von Winiwarter. Bunge, on the other hand, agrees with von Manteuffel, but his three cases appear to be instances of advanced arteriosclerotic change in elderly people, rather than examples of the disease grouped under the name "endarteritis obliterans."

Two schools, then, have arisen among those who have made careful anatomical investigations: first, those who agree with von Winiwarter and who attribute the closure of the vessels to proliferation of the intima; and, second, those who consider the process to be a peculiar type of arteriosclerosis in which desquamation of endothelium in the popliteal artery leads to the formation of parietal white thrombi and to occlusion of the arteries by direct peripheral extension from the primary focus.

During the past year I have had an opportunity of observing quite a large number of patients suffering from this disease, both in dispensary practice and in Mt. Sinai Hospital, and, through the kindness of Drs. Lilienthal, Gerster, and Sachs, have been able to make careful anatomical studies on ten amputated lower extremities. Although the results of the macroscopical and microscopical examinations of the vessels agree in a number of essentials with the findings of other authors, certain additional facts were obtained which throw new light upon the genesis of the process. From my own findings, I may anticipate now by saying, I can agree neither with von Winiwarter nor with von Manteuffel, and must express the view that we are dealing here with *thrombo-arteritis* and *thrombo-phlebitis* followed by organization and canalization, and not with an obliterating endarteritis.

Gross Pathology.

It is not my purpose to give you a minute and detailed account of the pathological lesions which underlie the clinical pic-

ture that I have described earlier in my paper. At present, I am able to report to you only the changes in the vessels, and must defer the results of the examination of the nerves until another time. Sufficient data, however, have been collected by me to warrant the assumption of a new theory in regard to pathogenesis, and I shall therefore confine my remarks to those important gross and microscopical lesions which bear directly upon my own conception of the process, reserving a complete discussion of the etiological factors for a future publication.

If we dissect out the vessels in these cases we are struck by the fact that there is an extensive obliteration of the larger arteries and veins. Besides this we find two other lesions which vary greatly in their intensity, namely, the periarteritis and the arteriosclerosis.

Upon making a large number of sections through such obliterated arteries and veins at different levels, we find certain characteristic appearances, which, in a general way, depend upon the age of the occluding process. Usually the vessel is seen to be filled with a grayish or yellowish mass that can be distinctly differentiated from the annular wall of the vessel, and that appears to be pierced at one point (more rarely at a number of points) by an extremely fine opening through which a minute drop of blood can be squeezed. Such obturating tissue is firm in consistency and does not at all resemble the crescentic or semilunar occluding masses of arteriosclerosis. The vessel itself is usually contracted so that its wall appears somewhat thickened. This picture is characteristic of arteries or veins which are the seat of a very old obliterative process, and is to be found most frequently in the peripheral portions of the vessels, although at times this type of lesion may extend throughout the whole length of the vessel, from the dorsalis hallucis almost into the popliteal.

As we trace certain of the obliterated arteries or veins upward, we are apt to meet with a change in the character of the obturating tissue; frequently it becomes softer, and more brownish in color, and terminates abruptly in the lumen of an apparently normal vessel; at other times the brownish tissue gives

way to soft reddish masses which are evidently the results of recent thrombosis. In some cases this thrombotic process occupies large portions of the vessel's course; in others, it is of short extent and terminates in a long cone of recent thrombus

It is interesting to note that the veins share equally with the arteries in the lesion of occlusion. In some cases the veins are more extensively involved than the arteries and this is particularly true of the collaterals of the posterior tibial which are often closed when the anterior tibial veins are open. As for the arteries, we usually find an obliteration of a part or the whole of the anterior tibial, of the dorsalis pedis and dorsalis hallucis, and occlusion of the posterior tibial and plantar vessels with or without involvement of the peroneal. Sometimes the anterior tibial is practically normal in its upper half or upper two-thirds. More rarely a large portion of the dorsalis pedis is open with the beginning of the occlusion in the upper part of this vessel, or in the lower part of the anterior tibial. It is to be regretted that the termination of the process in the posterior vessels of the leg could not be determined in every instance because of the fact that amputation was done at a point where the posterior tibial was closed. In two cases, however, the popliteal and part of the posterior tibial vessels were found free; in others the popliteal could be felt to pulsate before the operation, and we can therefore conclude that in a number of cases at least the obturation does not attain the level of the popliteal artery.

Without giving a detailed description of the extent of the occlusion in all the cases, we may summarize by saying that we usually meet with obliteration of large territories with closure of the distal parts of the vessels, rather than the proximal; that there is often an involvement of some of the smaller branches such as metatarsal and tarsal; but that the finest arteries are free. The beginnings of the obliteration are not to be sought in the capillaries nor in the finest branches. If we follow the vessels upward, we frequently see a sudden cessation of the process, and, in a number of instances, we find that some five or ten centi-

meters of a vessel's length are closed, and that the portions above and below are apparently normal.

It is from a study of the terminations of the obliterating masses of tissue together with a study of those parts of the vessels which are apparently unaffected by the process, that most valuable information in regard to the pathology of the disease can be gained. As already indicated, there may be a sudden and abrupt change from occluded vessel to normal vessel, that is to say, the yellowish brown tissue terminates in a rounded dome-like process which projects into an apparently normal lumen; or there may be a transition into red thrombotic masses or a conversion of the denser occluding tissue into tissue not unlike granulations. Such terminations occur at various points in the course of the arteries and veins. In one case the obliteration of the anterior tibial extended to about the middle of its course and above this point its walls were almost normal save for some thickening of the intima. In another case the upper and lower terminations of the occluding tissue were found in the posterior tibial and in the peroneal arteries.

From the peculiar appearances presented by these terminations, from the apparently normal condition of the vessel above and below the occluding masses, and from the transition into thrombosed areas, it would appear that we are dealing with a thrombo-arteritis or thrombo-phlebitis, rather than with a proliferative or obliterating process derived from the intima of the arteries and veins. The microscopical studies gave sufficient evidence of the correctness of this conception.

Besides the lesion of occlusion there are two other striking changes, namely, a certain amount of arteriosclerotic thickening and periarteritis. The arteriosclerosis is never pronounced except in those rare instances in which the patient has suffered from the disease for many years and has reached the latter part of the fourth decade. As a rule, we note but a very slight degree of whitening or thickening of the intima here and there in the patent portions of the vessels. There were deposits of lime in but one case, and these were of but small extent.

A much more interesting and more important change is the fibrotic thickening of tissues immediately about the vessels, which I wish to group under the name "periarteritis." Wherever the vessels are occluded there is apt to be an agglutinative process which binds together the artery and its collateral veins, and sometimes also the accompanying nerve, so that the liberation of the individual vessels by dissection is difficult. This adhesive condition is due to fibrous tissue growth and varies considerably in its amount. At times we find little or no change about the occluded artery, at times fairly firm agglutination of the vessels in the sheath, without much fibrosis, and at other times so large an amount of connective tissue growth that isolation of the vessels or nerves becomes impossible, and the vascular structures make up one dense rigid cord. In a general way we may say that whenever both the collateral veins and the artery are occluded, we expect a fair amount of periarteritis, and that when but one vessel is affected the perivascular change may be insignificant; and, finally, that the amount of periarteritis varies in the different cases as well as in the different territories affected by the disease.

Histology.

The pictures presented by the vessels involved in this process are so varied that I must needs confine myself to the description of those rather typical changes that have suggested the true nature of the process to me, and from a study of which we can see the development of the lesion from its incipiency to its final maturation. I wish to point out, first, the lesions of arteriosclerosis; second, those that belong to periarteritis; third, the typical pictures found in the old obliterative process; fourth, the differentiation of this lesion from the occlusive changes of arteriosclerosis; and, fifth, the various stages in the development of the occluding process from the beginning of the thrombosis to the final filling up of the vessel with dense fibrotic masses.

Both the arteries and the veins show varying degrees of thickening of the intima, the usual subendothelial changes with a fairly well marked hypertrophy of the internal elastic lamina

without much proliferation of new elastic tissue in the thickenings of the intima. Of the two types of elastic tissue production pointed out by Jores, that which is dependent upon reduplication or hypertrophy of the internal elastic lamina is the more pronounced. Now and then in the older patients there are small plaques. Although the very small arteries may also be the site of thickening of the intima, this change is never sufficiently great to lead to complete or even marked obliteration of the lumen of the vessel. In the popliteal artery the formation of nodular thickenings is most extensive, but even here these are of moderate size.

The periarteritis manifests itself in a proliferation of connective tissue in and around the adventia, and is of two types, recent and old. Where the perivascular proliferation is active, the fixed connective tissue cells multiply and fibrous intercellular substance is deposited. Here and there small perivascular foci of lymphoid cells are found, but these do not seem to take an important part in the formation of connective tissue. In the old variety, the fibrotic process appears to have come to a standstill, and the vessels and nerves are encased by dense bands of fibrous tissue, sometimes of a hyalin nature.

If we examine a cross section of an artery or vein which is the seat of an old obliterative process, we often find an irregular, centrally placed lumen, a large amount of new formed tissue occluding the original lumen, and certain changes in the media; the whole picture giving the impression that there is an extensive proliferation of the intima, namely, an endarteritis obliterans. From a consideration of the descriptions which are to follow, we will understand, however, that the new masses in the lumen are not derivatives of the intima, but owe their origin to organization of obliterating red thrombi. In the occluding tissue we find a fairly large number of capillaries, some blood pigment, and fibrous tissue which is either rich in cells or has already become sclerotic in nature. Where the process is oldest, there the capillaries are few, the connective tissue has become dense, the pigment has disappeared, and either in the middle or near the periphery of the obliterating mass, there is a large dilated vessel

which is surrounded by connective tissue, and which simulates the remnant of the original lumen. In other vessels, there are large sinuses in the occluding mass, or dilated vessels separated by dense connective tissue; or there are atypical conformations in which two large blood spaces are separated by a septum that appears to spring from the intima of the vessel. The internal elastic lamina is thrown into marked folds and between it and the connective tissue described, there may be a slight or moderate amount of fibrotic change in the intermediate layer of Eberth. The striking lesion of the media is the presence of capillaries with or without a small amount of lymphoid infiltration in their immediate vicinity. Such capillaries may be present in small or in large numbers depending upon the age of the process; where the occlusion is recent, the signs of activity in the media are striking, the capillaries plentiful, the cellular infiltration marked. The fine vessels come in from the adventia, pass through the media, and penetrate the internal elastic lamina in order to vascularize the obturating mass.

What are the distinguishing features which enable us to differentiate an arteriosclerotic process from the lesions just described, and how can we establish the independence of the obturating masses from th intima, from which most authors would have them arise? By the employment of the elastic tissue stains, certain characteristics are brought to light which make it possible for us to say whether we are dealing with a thickening of the intima or with a new tissue lying in the lumen of the vessel. In arteriosclerosis we often find large obturating plaques which almost completely fill the vessel, the small space that is left being finally closed by a thrombus which becomes organized. It is not difficult to recognize such lesions as being arteriosclerotic when we note the large amount of elastic fibers in the plaque and note that these fibers are disposed for the most part parallel with the internal elastic lamina. In the occluding masses of so-called endarteritis obliterans, we find either a total absence of elastic fibers, or, when such are present, a growth of fibers around the larger canalizing vessels, particularly about those which are thick walled

and old. The differences in the two lesions are well elucidated by the pictures which we obtain when we examine vessels that show a combination of marked arteriosclerosis and so-called endarteritis obliterans. At times we find an occlusion of a vessel by obturating masses at the site of an arteriosclerotic plaque, and then the distinctions which I have pointed out become very apparent. Some of the photographs which I pass around for your inspecitis obliterans. At times we find an occlusion of a vessel by obturating tissue and intima, this will be better established when I have discussed the stages in the development of the process. Here I may simply mention the fact that the elastic tissue stains also show that it is only where a capillary penetrates the internal elastic lamina to vascularize the obturating tissue, that there seems to be any direct connection between the two. The elastic fibers that belong to the thickened intima never pass over into this tissue except in those rare instances where the penetrating vessel has ruptured such fibers and has carried them for a short distance inward.

The most instructive histological pictures are those that are obtained in an examination of the vessels that are closed by transitional occluding tissue, and by this I mean obturation due to red thrombotic masses which can be traced into the softer brownish tissue and which finally may terminate in the dense old masses, the histology of which has already been discussed. In a number of cases, and especially well marked in the vessels in an extremity which was amputated because of pain without gangrene, such transitions from areas of red thrombosis into the older stages were found. If we examine a vein or artery at or near the termination of the red thrombus, we find a fairly recent clot filling the lumen of the vessel without change in the vessel wall. A short distance further the clot becomes adherent in places and the corresponding portions of the media show beginning lymphoid infiltration and the earliest signs of vascularization. At a point still further removed, the aspect of the thrombosis has considerably changed. A number of miliary foci, not unlike miliary tubercles, make their appearance near the periphery and there are

evidences of organization, such as the formation of capillary sprouts, fine capillaries and fibroblasts. The miliary foci present a central area of fibrin and one or more giant cells (probably phagocytic in nature) with cells not unlike endothelial cells in a peripheral zone. Such giant cell foci are but early stages in the process of organization. At another level the picture changes; the miliary foci gradually become lost; the vascularization of the clot becomes marked; the fibrin is almost absent; and numerous small round cells are scattered throughout. Here the media also shows quite a number of small capillaries with or without perivascular lymphoid infiltration. While the fine vessels in the thrombus at this level are thin walled, we soon note a change in their character. They become longitudinally disposed; here and there they connect with the media; they are surrounded by numerous round cells and fibroblasts and some blood pigment. These latter pictures correspond to the tissue which appears brownish and is not very firm. From this point on, the transition into the old type is fairly rapid. The cells in the obturating mass disappear and the fibrous intercellular substance becomes abundant; some of the capillaries atrophy; others become dilated, forming large spaces with well defined walls; at times there are numerous sinuses giving a fenestrated appearance; at times there is a centrally placed vessel resembling a much diminished lumen of the original vessel and sometimes such canalizing vessels are centrally placed. With this final maturation of the organizing process there are certain concomitant regressive changes in the media, namely, a diminution in the number of capillaries and the disappearance of alien cellular elements.

A detailed discussion of all the bizarre appearances that were found would take me too far, and I have therefore alluded only to those changes which seem to me to be valuable in clarifying the cause of the occlusion and which show that this is to be sought not in an endarteritis, but in the organization of red obliterating thrombi. I have described in brief the stages in the development of the process, and have shown how the old typical pictures can be directly traced into the areas of old and recent thrombosis,

and, further, how the changes in the media are dependent upon vascularization of the clot and are not primary. What other evidences have we to establish the correctness of our view of the process? A histological study of some of the terminations of the obturating tissue, particularly of the abrupt variety gives valuable information on this score. Thus if we make longitudinal sections through these rounded ends of occluding tissue which mark the cessation of the process in some of the vessels, we see how the closed portion of the vessel surrounds a vascular mass of young connective tissue and pigment; we note how the end of this mass rounds off, that it seems to be wholly independent of the intima except for points of junction by means of penetrating capillaries; and we are struck by the absence of pathological lesions just beyond the point of closure.

Finally, we must interpret the nature of those pictures which would at first sight be mistaken for obliteration due to proliferation of the intima; namely, those in which there is a large canalizing vessel more or less centrally placed, surrounded by a fair amount of elastic fibers. The paucity of elastic fibers in what would appear to be thickened intima, and the fact that the apparent remnant of the original lumen of the vessels usually divides at other levels into a number of smaller blood spaces, many of which finally communicate with the media, make it evident that we have here simply another product of the organizing thrombotic process.

Granted that we are dealing with a *thrombo-arteritis* and *thrombo-phlebitis obliterans* or *productiva*, how are we to explain the cause of the thrombosis? What role does the arteriosclerosis play in the lesion, and in what manner are the arteries and veins first affected? In view of the absence of completed studies on the nerves, the time is not ripe for any positive expression of opinion. We would at first hand be led to the belief that the changes in the intima are in great part responsible for the thrombosis. For this is doubtless the case in the secondary closure by clot in cases of senile and diabetic gangrene. Indeed, Zoege von Manteuffel takes the view that parietal white thrombi first lodge

in the popliteal and gradually extend downward; that they remain mural in nature, are of the white variety, and are rarely mixed with small red clots of recent origin. Practically every one of my cases furnished me with many evidences of the incorrectness of this conception. Thus the large territories filled with red thrombi with their transitions into the old occluding masses, the frequent absence of any change in the upper parts of the anterior tibial and posterior tibial when very distant parts were occluded, and, further, the presence of pulsation in the popliteal in some of the cases in which that vessel could not be examined: all these speak against his assumption. We gain the impression that the obturation ascends rather than descends; for the firmest and oldest tissue is most frequently found in the distal parts and not infrequently terminates in young thrombi or soft rounded abrupt terminations in the middle or lower part of the leg. Finally, the presence of the same lesion in the veins, which Zoege von Manteuffel had evidently not encountered, could certainly not be explained in the light of his theory.

Viewing the process from the standpoint of the pathological lesions, and considering certain facts obtained by clinical observation, it would seem most plausible to assume that certain territories, of either the arteries or the veins, become rather suddenly thrombosed, in a fashion similar to the thrombotic process which occurs in the superficial veins of the lower extremities. Thus at one time the dorsalis hallucis and dorsalis pedis, or perhaps the plantar arteries or veins, could become closed by red clot; and then the process of organization would take place. Perhaps after an interval of weeks or months, a similar process would cause extension upward, or affect other arteries and veins, until, after a lapse of many months, or a year, or more, practically all the larger vessels would become occluded. It is from a study of the age of the process in the various territories that we are led to this supposition. Here, too, as in the superficial thromboses, there is more tendency for the larger vessels to be involved than for the very fine ones; and, although the process seems to ascend, it probably does not originate in the capillaries or smallest

arterioles, but begins in branches of moderate size. The attendant periarteritis could be regarded as being either secondary or possibly as being produced by the same causes that lead to the thrombosis. Certain it is that the periarteritis is intimately linked with the presence of occluding masses.

In the future study of the etiology we ought to pay close attention to the rôle that syphilis may play in the production of these lesions. In none of the cases was it possible to obtain a definite syphilitic history, nor did they show any of the characteristic stigmata. Even the histological pictures leave us in doubt. Whatever may be the cause of the thrombosis, we feel inclined to take the view that, although the mechanical conditions that obtain in the lower extremities and the arteriosclerotic changes may be factors, some additional causative agent, be it toxic or otherwise, is at the same time responsible for the production of the periarteritis and of the thrombosis.

Taking the true nature of the lesions into consideration, I would suggest that the name "endarteritis obliterans" be no longer applied to the pathological changes under discussion, and that we adopt the terms *thrombo-arteritis* and *thrombo-phlebitis obliterans,* or, to be more concise, *thrombo-angeitis obliterans* or *productiva.*

I wish to express my indebtedness to Dr. F. S. Mandlebaum, Director of the Pathological Department of Mt. Sinai Hospital, for the preparation of the photomicrographs which I have shown to elucidate certain points in my paper. I wish to thank Drs. Lilienthal, Gerster and Sachs, for according to me the opportunity of studying their cases, and to acknowledge with pleasure the valuable assistance rendered me by Miss Adele Oppenheimer and Dr. Mark Cohn, volunteer assistants in the Pathological Department of Mt. Sinai Hospital.

Discussion.

Dr. H. Lilienthal said that he could say nothing about the pathology of this extremely interesting condition. He thought that there was not much left to add; as far as accurate scientific

observation of cases goes, Dr. Buerger had pretty completely covered it, with the exception, as he had said, that study of the nerves might throw some light on the subject. Clinically, he might be able to add a word. These cases were seen at the Mt. Sinai Hospital in greater numbers probably than anywhere else in America. For this there must be some reason. Perhaps there was a poisoning of some sort; possibly due to eating rye bread which was ergotized. It was certain that in a person who had a tendency towards the disease, or had it in its incipiency, the use of tobacco accelerated the course of the disease. Dr. Lilienthal spoke of the case of one man who had the disease of the arteries, who was in wretched general condition, and who finally had to have his leg amputated on account of gangrene. He had been an inveterate smoker and was advised to stop smoking entirely, which he did. A year after, his appearance was wonderfully changed. He reported that the pains which had begun in the other leg had practically disappeared, that the pain in the stump of the amputated leg had diminished, and that he was tremendously improved. This in spite of the fact that before amputation he had taken all sorts of drugs in the hope of warding off the trouble. It was an interesting clinical fact also that in spite of the obliteration of the arteries the bones of these patients heal very nicely. In a number of cases Dr. Lilienthal had performed osteoplastic operations, covering the bone marrow with a little piece of bone which remained attached by periosteum as by a hinge (Bier's method). The method had been found to work perfectly well. Even in a leg in which there had been gangrene one could perform the osteoplastic operation; the circulation in the bone seemed to be good enough to give perfect union. A man at present under observation had been operated upon in this manner, and in spite of the fact that there was a little spot of necrosis of the bone there had been no breaking down. Dr. Lilienthal felt sure from past experience that the wound would eventually heal entirely. One would think that in so ill-nourished a tissue as a little piece of bone attached only by a flap of periosteum, if the arteries were all diseased, union would not take

place. He thought there must be some difference in the arteries in the bone, and asked Dr. Buerger if he had decalcified the bone and examined the arteries. A sad part of these cases was their occurrence in young people; he had had patients as young as twenty.

Dr. T. C. Janeway asked Dr. Buerger whether he had made any observation on the relation of the venous thrombosis to the clinical type with cyanosis. Did that represent a later stage of the process?

Dr. I. Levin congratulated Dr. Buerger on the thoroughness of his study. From the standpoint of pathology, he thought it the most thorough study which had been made on the subject. Dr. Buerger's conclusions seemed at first to be entirely original. There were a number of different theories held in regard to this condition. There is a school that considers proliferation of the intima as the primary cause. There is a school that considers that while the primary condition is a disease of the intima, still the thrombus formation is the real cause of the gangrene. Some writers consider the media as the primary cause of the disease, and Dr. Levin had somewhat come to the same conclusion. Dr. Buerger seemed to consider that the primary condition was the formation of the thrombus, but Dr. Levin did not understand how he explained the formation of a thrombus in a healthy vessel with healthy walls. The understanding in pathology was that thrombosis would occur only through embolism, or else through a diseased wall of the vessel. At the end, Dr. Buerger had said that he thought some kind of intoxication or disease of the intima must have occurred before the thrombosis took place. If that were so, the difference between his opinion and that of others would not be so great. It seemed to him that we could not very easily exclude any part of the wall of the vessel in that diseased condition. There was most probably a disease of the whole vessel wall, whether it were most marked in the intima or in the adventitia. It seemed to him that while in the majority of Dr. Buerger's cases the most important factor had been the thrombus formation, one photograph which he had explained as thrombus

with canalization in the center, looked more like real proliferation of the intima without any thrombus. The canal of the blood vessel instead of having a circular form showed a rather narrow broken formation. As regarded the clinical side of the question, Dr. Levin wished to say a word about the rye bread which Dr. Lilienthal had mentioned. The works on this subject showed that the disease usually occurred in Russian Jews, and not in Russian Gentiles; the Russian Gentiles, however, eat only rye bread.

Dr. B. Lapowski asked whether, when Dr. Buerger spoke of a fresh thrombus forming independent of the vessel, he meant that the vessel wall at that point was not changed. If the intima was changed, there was no difference between his and Zoege von Manteuffel's opinions. The formation of the primary thrombus in such cases may be due to the changes. Dr. Buerger spoke of an acute formation of thrombus in the wall; but this would not answer to the clinical picture. Usually the clinical picture lasted for years. Dr. Lapowski said that cases of the disease had been reported in Russian Gentiles. The disease had been ascribed to severe cold. Probably 98 per cent. of the cases reported were among Russian Jews, but this was because the doctors (Goldflam, Higier, Idelsohn, Erb) who describe the cases have a practice among those people. As regarded syphilis, Dr. Lapowski did not agree with the opinions expressed. He had seen several cases which had responded to mercury though there had been no direct manifestations of syphilis. He thought every case should be treated for syphilis and then carefully watched. If there was any improvement, the treatment should be continued, for years if necessary, before amputation. One of the cases mentioned was under the speaker's care, and was improving under syphilitic treatment; the gangrene of the fingers had entirely disappeared, the fingers assuming their normal aspect; and the ulcers on the toes were also improving, though more slowly. If the treatment had had a longer trial the former amputation would have been unnecessary.

Dr. J. H. Larkin hoped that even the thorough work which

Dr. Buerger had done would not be accepted as final. Not long ago Dr. Levin had presented a case which had aroused a great deal of discussion. Thorough dissection of that leg showed conditions which were at great variance with the conclusions given by Dr. Buerger. He did not think very much of the photographs as proving the points. He did not think that as regarded the pictures one could at all leave out the connection of the intima and thrombus formation. In Dr. Levin's case there had been a great amount of endarteritis; the musculature also played a very important part. Dr. Buerger's remarks about organization of the thrombus as derived from proliferation of the connective tissue from the media, leaving out the intima, seemed to touch on a very difficult point.

Dr. A. V. Moschcowitz thought that Dr. Buerger, Dr. Levin, and Dr. Larkin might all be right. In the various cases of gangrene there might be different findings. Clinically the cases differed very much. Some patients feel pain when the leg is in the pendent position; others when the leg is elevated. Some cases present marked pain when the foot is cyanotic; others when it is pale. It seemed to him that these points could be very well brought together. Moszkovitz, of Vienna, had brought up the question where to operate. The speaker had tried the method, which might be of interest to the Society. An ordinary Esmarch bandage was applied and the leg was elevated. After the elastic bandage had been on for three or four minutes it was taken off. When the hyperemia returned it usually showed a sharp edge; that was the place where the amputation should be done. Amputation above that line was usually unnecessarily high. If the amputation was done below that line there was apt to be secondary gangrene of the stump.

Dr. E. Libman though that it was a cause for congratulation that a subject had been found which was of interest to the clinicians as well as to the pathologists. On looking over the constitution recently he had found that the objects of the Society were stated as "the advancement of the knowledge of pathological anatomy, histology, and general pathology, and the improve-

ment of its members in these departments, and in the diagnosis and treatment of disease as founded upon them." He thought that it would be wise to have clinicians and surgeons interested in the work of the Society.

Dr. Buerger said, in answer to Dr. Lilienthal's question as to whether he had examined the vessels in the bones, that he had not included these in his study because he did not think that the small vessels would be affected by the obliterating process, inasmuch as they usually showed only a moderate degree of arteriosclerosis elsewhere. He thought that a number of gentlemen who had discussed his paper had failed to see that he wished particularly to bring out the fact that the lesion in the vessels was one due to thrombosis and not to endarteritis. Hence Dr. Levin's statement that the views of other authors were not so very different from the one suggested by him. He could readily see how Dr. Levin could be mistaken in the interpretation of certain of the photographs presented, for the picture produced by an obturating process arising from the intima, and that produced by canalization of a thrombus, may be so similar that only the elastic tissue stains and the study of the future course of the central canalizing vessel would clear up the nature of the process. In reference to Dr. Larkin's remarks, Dr. Buerger pointed out that the slides which he exhibited showed much better than the photographs the various stages in the development of the process. Dr. Janeway had asked whether there was any relation between the pathological findings and the clinical symptoms, as far as the ischemia and cyanosis were concerned. Dr. Buerger remembered one case in particular, in which there was marked involvement of the veins and in which the erythromelalgic and cyanotic symptoms were very pronounced. Many of the superficial veins were thrombosed in a manner similar to the deep vessels. Possibly the cyanosis is of greater degree whenever the veins are markedly diseased. The case which Dr. Lapowski had described, had been carefully observed by the speaker for about four years. In this patient the disease commenced in the upper extremities as a migrating phelbitis extending in quick succession upwards

through the superficial veins of the forearm. About four years ago a piece of one of the thrombosed veins was removed at Mt. Sinai Hospital, and Dr. Mandlebaum, the pathologist, reported the lesion as being an obliterative thrombo-phlebitis, possibly syphilitic in nature. Curiously enough, this patient developed the typical symptoms in both lower extremities, the erythromelalgic signs, coldness, pain, and trophic disturbance. In addition, however, he had frequent attacks during which the superficial veins of the lower extremities became thrombosed. It was more than probable that the deep vessels of the leg were affected by a process similar to that which had first appeared in the upper extremities.

In analyzing the literature, Dr. Buerger said, we must not become confused by statements regarding thrombosis in the arteries in cases of gangrene. Careful investigation of the findings of most authors reveals the fact that many of the important instances of thrombosis occurred in patients suffering from marked arteriosclerosis in which a secondary thrombosis had taken place. Dr. Buerger did not wish to convey the impression that all cases of spontaneous gangrene of the lower extremities in young people were due to the same cause, or were of the nature he had described, and he therefore did not question that the media was the seat of disease in Dr. Larkin's case. Finally, he said, we should not place too much reliance upon the Moszkovitz test because it demonstrated the patency of collaterals rather than of the original vessels, and it must be remembered that the collateral could at any time become closed and the nourishment of the part could suddenly become impaired.

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Dr. E. Libman, *President.*

COLON IRRIGATIONS IN THE TREATMENT OF PERNICIOUS ANEMIA.

G. R. SATTERLEE, M. D., AND S. O. SABEL, M. D.

Dr. G. R. Satterlee reported for himself and Dr. Sabel two cases of pernicious anemia which had been treated with colon irrigations.

The first case was that of a male, forty-four years of age, who entered the Washington Heights Hospital on October 16, 1907, suffering from indigestion, palpitation and dyspnea. There was

no history of syphilis or gonorrhea; the patient drank in moderation. He had not been ill up to two years before. He then had had bronchitis for four months, which had been treated without relief. This was followed by intestinal troubles and severe diarrhea. He lost weight and noticed a peculiar greenish color of the skin. He had spots before his eyes and for one and a half months was totally blind; he also had palpitation of the heart. Under treatment he improved up to three months before admission when the symptoms returned.

Physical examination showed a picture characteristic of severe anemia of pernicious type. The mucous membranes pale, sclera pale, pupils normal. There were evidences of stomatitis and glossitis, and the edges of the tongue were raw. No glands were palpable except in the inguinal region. The spleen was just palpable. Blood examination showed red cells 2,980,000, leucocytes 12,000, polynuclears 51%, lymphocytes 49%; no eosinophiles. Blood smears showed megaloblasts, microcytes, and marked poikilocytosis. The patient was put on a bread and milk diet with administration of egg albumin and ferric chloride. The chief symptoms while in the hospital were vomiting, diarrhea, and offensive odor to the stools; no parasites were found. Sputum contained no tubercle bacilli. The urine was of a specific gravity of 1.020 to 1.025, and contained a trace of indican. The patient's condition grew worse and he complained of disagreement of medicine, so that all drugs were stopped. Colon irrigations were begun on October 3, normal saline solution being used. The stools were very foul and contained blood and undigested food. Marked improvement was at once noticed and in four days the patient was out of bed. Gastro-intestinal symptoms continued. The only treatment from this time on was colon irrigation. Blood examination showed gradual increase of red cells and percentage of hemoglobin and polynuclear leucocytes. During the last week of his life the patient grew worse and had a severe cough. Temperature during the course of his illness was above normal, for

part of the time 102° or higher. Just before death he had an hemoptysis. Autopsy showed hydrothorax, hypostatic pneumonia, hyperplasia of lymphoid follicles, dilatation of the heart, right side, atrophy of the bone marrow of the ribs and vertebrae, dilatation of the stomach with a double stenosis, giving a triple sacculated appearance to the organ as seen in the specimen presented. Microscopically the mucosa showed an infiltration around the glands of round cells and fibrous tissue. The spleen was enlarged two and one-half times. There was chronic interstitial hepatitis, chronic interstitial pancreatitis, chronic parenchymatous nephritis. Both large and small intestines were congested; no parasites or ova could be found; no ulcerations. Microscopical examination of the bone marrow from the femur showed a large number of nucleated red cells, diminished proportions of bone marrow cells, no eosinophiles or fat cells.

The second case was that of a woman, fifty-five years of age, admitted to the Washington Heights Hospital, June 21, 1907. The patient's history showed a long period of constipation with much gastric trouble. No bad habits, no syphilis. The patient complained of chills, weakness, vomiting and constipation. Physical examination showed pronounced anemia. Blood count gave red cells 1,940,000, hemoglobin 26%, leucocytes 6,200. There was a large proportion of megalocytes with few microcytes and polynuclears. No nucleated red cells appeared at first. Special features were flatulence, vomiting now and then, extreme weakness and constipation. There were a few hyalin casts and red blood cells in the urine. There was marked brownish pigmentation of the skin and general desquamation. Colon irrigations were begun July 23 and were continued until two weeks before the patient left hospital with marked improvement; hemoglobin quickly rose to 50%; red cells increased; nucleated reds disappeared.

Conclusions:—The predominating symptoms in these cases were not only those of severe anemia of pernicious type, but also

of severe gastro-intestinal troubles. Both cases started with intestinal disturbances. During the colon irrigations the symptoms and general conditions were improved; but in case 1 they were begun too late to be of avail. In the second case the symptoms were markedly improved If the disease is due to an intoxication colon irrigations would seem to be a rational way of treating, if not of curing, it; but if begun too late would be, of course, of doubtful efficiency.

Hunter had concluded that pernicious anemia is a specific condition resulting from excessive hemolysis; in 1907 he stated that it was an infective disease localized in the intestine. The gastric lesions were considered by Hunter as the seat, not only of the primary infection, but also of its development. Herter has shown that the presence of certain forms of bacteria breaks down proteids suitable for the use of other putrefactive organs, and that putrefaction is responsible for indican.

Drs. Hollis and Ditman have reported two cases of pernicious anemia treated by colon irrigations with very marked improvement. Dr. Hollis had since stated that the first case had died because of drink, and the second case had a relapse through overwork and was again under treatment.

The two cases of Dr. Satterlee's were reported in the hope that they might be of help in determining the etiology and mode of treatment of this disease.

Discussion.

Dr. F. C. Wood said that he had followed the cases reported by Drs. Hollis and Ditman, and at the time of their report had called their attention to the fact that the blood still showed the type of pernicious anemia. The cases were merely in the stage of marked remission. One case had already died, and the other case was now in St. Luke's Hospital and was practically moribund. Dr. Wood had seen two other cases, one a woman followed

for three years, who had been faithfully treated with colon irrigations and who showed only slight improvement for short periods, and finally died. She had never done any work and had taken good care of herself. The other case was that of a business man on whom the irrigations had produced not the slightest effect. While the blood examinations showed great variations the changes were not at all connected with the colon irrigations, which he had kept up regularly. Dr. Wood thought the improvement seen in many of the cases might be due entirely to the increased peristalsis and improved nutrition, and not necessarily to the removing from the bowel of hemolytic toxic substances.

Dr. James Ewing said that recently Dr. Schaffer had examined for him the stools of a prolonged case of pernicious anemia, two days before death, when the hemoglobin was about 8%. He was unable to determine any increase in the ordinary putrefactive products of the intestine, as indol, skatol, and phenol.

Dr. Satterlee said in regard to Dr. Wood's cases that of course, where one got pernicious anemia late in the disease the colon irrigations were hopeless. It was only in the beginning of the disease that they might have some effect.

A CASE OF PRIMARY CARCINOMA OF THE LIVER.

F. C. WOOD, M. D.

Dr. F. C. Wood presented specimens from a case of primary carcinoma of the liver which showed very well the gross lesions of the condition. The specimen was removed from a case dying at the German Hospital. An exploratory laparotomy had been done on the patient who was supposed to have either gall-stones or a secondary carcinoma. The symptoms were jaundice and a large liver, together with failing strength. A small piece of the

liver was excised at the time of operation and the diagnosis was made. The patient died about a week after the operation. Dr. Wood had seen only three of these cases of primary carcinoma of the liver in his experience, all showing about the same type of tumor. Sections of the nodule showed a tumor which varied a great deal. Some portions were adenomatous; others differed considerably from the normal liver cell and might be properly considered as carcinoma. There were, of course, degenerative and other changes in the liver cells which were often of large size. The diagnosis of adenocarcinoma was suggested. There were many mitoses in the tumor tissues. There were no metastases found, metastases being rare in this type of tumor. Under the microscope the sections showed fatty changes in the tumor cells and other cells of the liver. It was striking that there was practically no cirrhosis of the liver, and also that the liver cells were of enormous size, two or three times the size of normal liver cells.

The case will be published in full later.

NOTES ON ARTERIOSCLEROSIS OF THE PULMONARY ARTERIES.

HANS ZINSSER, M. D.

Although the occurrence of vascular disease in the pulmonary circulation is by no means a rare phenomenon, there are many factors in its relation to similar disease in the systemic circulation, which have seemed to justify the presentation of the subject to this Society.

Since 1850 and the years following, when the condition was first described by Dittrich and Bamberger, the number of cases of the lesion reported has rapidly multiplied, the various authors agreeing with more or less emphasis that arteriosclerosis in the

smaller circulation is in some way related to the increased intravascular pressure accompanying cardiac disease, especially disease of the mitral valve. The frequency of the disease, however, has been, even to the present day, a matter of controversy, von Schrötter, as recently as 1899, claiming that the lesion was of comparatively rare occurrence. Brüning, who carefully studied a series of twenty-one cases, reached the conclusion that the lesion is much more frequent than is generally supposed, and that even in cases where no macroscopic disease is demonstrable, microscopic examination may reveal lesions in the smaller vessels.

The questions which arise with particular insistence in the study of this lesion are, first, in how far do these changes in the pulmonary vessels depend upon the local influence of intravascular pressure due to cardiac disease? and, second, how closely is the lesion dependent upon co-existent disease in the systemic circulation?

In the course of the past few months the writer has had occasion to note the occurrence of pulmonary artery atheroma in fifteen cases, which may be briefly summarized. A large number of these were placed at the disposal of the writer by Professor Hodenpyl of the College of Physicians and Surgeons.

Of these, nine were cases of mitral stenosis, six of marked, three of moderate degree.

Five of these cases showed extensive lesions of the circumscribed variety of atheroma, patches extending into the very smallest branches that could be macroscopically examined. Microscopic examination of these cases, by the Sudan III frozen section method, showed fatty degeneration apparently beginning in the media, in other vessels involving the subendothelial layers of the intima. The changes noted consisted chiefly in thickening of the coat involved by a proliferation of delicate connective tissue in which the nuclei were abundant and the fibrils delicate and apparently loosely arranged. In all of the lesions, fatty degeneration of marked degree was present. Calcification was never noted.

Accompanying the fatty degeneration, there was usually seen young proliferating connective tissue with thickening of the vascular walls.

Other specimens, run through by the usual histological methods, showed no demonstrable lesions in the very small branches. In but one of these cases were similar patches noticed in the pulmonary veins.

The other four cases of mitral stenosis showed macroscopic lesions of only moderate degree, but still extending into the tertiary and further bifurcations of the pulmonary arteries.

Eight of the nine cases showed aortic atheroma; but in all but two of these the aortic lesion was insignificant, and in no way comparable in severity to the lesion in the pulmonary vessels. Two of the cases showed thrombi in the pulmonary vessels with infarction.

Of the remaining six cases, four were cases of chronic nephritis with marked aortic atheroma; two were cases of old subjects with myocarditis and cardiac dilatation. It was noteworthy that one of the nephritis cases showed the most extreme degree of aortic ulcerative lesions with but slight changes in the larger branches of the pulmonary vessels.

Through the courtesy of Dr. Hodenpyl, two other cases of unusually severe aortic lesions were examined, neither of which showed any lesion in the pulmonary circulation. As much of the material from which these data were taken came from the Morgue, little information as to previous history could be obtained, and the question of syphilis, rheumatism, etc., can not therefore be considered. Of four cases which came from St. Luke's Hospital, and of one which was kindly given to the writer by Professor Wood from the German Hospital, histories were obtainable. Only one of these, one of the mitral stenosis cases, gave an unquestionable history of syphilis.

To sum up the observations in these cases, then, all the mitral stenosis cases examined have shown the lesion of the pulmonary

vessels to a more or less extreme degree. In none of the cases was there any relation between the severity of the lesions in the aorta and in the pulmonary vessels. In none of the cases in which there was no cardiac disease with consequent increased intravascular pressure was the lesion at all extensive. None of these observations, the writer is aware, are particularly new; but they support in the main the statement of other writers.

Histologically, the conditions found correspond with those observed in similar cases by Thorhorst, Brüning, and others, differing only from the observations of the last named author, who found the smaller branches often diseased when no macroscopic lesions existed in the larger trunks.

The cases studied, as a whole, bear out the close relation of the lesion to mitral stenosis and the consequent pulmonary congestion, and the independence of the pulmonary vascular disease from the condition of the systemic vessels. This fact has been a source of much theorizing. Von Schrötter after studying the pulmonary and systemic arteries carefully found no histological differences in vessel structure to account for it. Rosenbach attributed it to the pulmonary circulation obtained from the respiratory movements of the chest, which facilitated the circulation through this system. The reason for the independence of the lesions in the two circulatory systems from each other is made clear by the work of Tigerstedt, Gerhardt, etc., who have shown that in order to increase appreciably the pressure in the pulmonary circulation, the systemic pressure must be raised to almost double the normal.

Two cases observed at St. Luke's Hospital, however, are of special interest. Both of these cases—old mitral stenoses—were accompanied by pulmonary thrombi with infarction. In neither of them could thrombosis in other vessels be found, nor had it been clinically suspected. In one of them there were recent vegetations upon the tricuspid valves. Cultures from the pulmonary thrombus in one of these cases showed Bacillus coli (the autopsy

was not done until six to eight hours after death); in the other case, cultivation was unfortunately omitted. In the absence of traceable source for embolism, without sepsis, and with marked arteriosclerotic changes in the pulmonary vessels, together with marked chronic congestion, it did not seem unreasonable to consider the possibility of a predisposition to pulmonary thrombosis brought about by the marked disease of the intima of the blood vessels.

Discussion.

Dr. E. Libman said that he thought the question was one of great interest. He had been making notes on these cases for some years, and had for a long time been looking for a case like the one described by Romberg of extensive atheroma of the pulmonary vessels. The clinical diagnosis in this case was congenital cardiac disease, and the patient had arteriosclerosis of the pulmonary vessels only.

A CASE OF TYPHOID BACILLI IN THE GALL-BLADDER.

HANS ZINSSER, M. D.

S. P., married, forty years old, admitted February 10, 1907. *Past history*: measles, scarlatina, pertussis, as a child. *Personal history* (procured later by the House Physician): illness sixteen years ago, probably typhoid. Three years ago some obscure gastric trouble lasting two months. Chronic constipation. Two months before admission, the patient began to feel run down, and lost her appetite; constipation increased; and she complained of pains in the abdomen. She did not at this time vomit, but was frequently nauseated. This continued until one or two weeks

before admission, when she noticed jaundice which since then has been steadily deepening. At the same time there was tenderness over the gall-bladder region and over the appendix. The edge of the liver could be felt and was tender. The stools were light in color, the urine dark. On admission, her temperature ranged from 101° in the afternoon to 98° in the morning, for about four days; it then quickly ascended until on the afternoon of the seventh day it reached 104°. The blood count showed 8,400 leucocytes, 74% of which were polynuclears. No bile was found in the stools, but there was a great deal in the urine.

On February 21, the patient was operated upon. The gall-bladder was found to be distended with pus, and a gall-stone, the size of a hickory nut was removed from the gall-bladder.

Synopsis of Autopsy Protocol:—The body was deeply jaundiced. Heart normal; pericardium contained bile stained exudate. The lungs were congested and edematous. The gall-bladder was dilated with a large quantity of bile and blood, and measured 8x6 cm. There was marked dilatation of hepatic and cystic ducts. The common duct was normal in size. Just beyond the entrance of the cystic duct into the common duct, there was a stricture, apparently old, containing small concretions. Next to the strictured portion of the duct there was a hard mass, the size of a hickory nut, which looked like an enlarged gland. At autopsy the stricture was thought to be benign, but section of this portion of the duct revealed carcinoma.

Bacteriological Findings:—In the pus in the gall-bladder, a bacillus was found in pure culture which later turned out to be a typical Bacillus typhosus. In smears from the pus and in the first transplants from this pus, the bacillus appeared extremely short, fragmental, and coccoid, the morphology being more like that of one of the members of the colon group than like that of Bacillus typhosus. The motility was very slight, though distinct, very much less than in the average typhoid culture as observed in the laboratory.

The interesting point in the study of this bacillus was the fact that, it being probable that the bacillus had dwelt in the human body for sixteen years, there were practically no important cultural changes in the micro-organism. Its sugar fermentations were entirely unchanged, in that fermentation took place with acid formation in dextrose, levulose, galactose, mannit, maltose (late), and dextrin; but not in lactose and saccharose. Gas was not formed on dextrose, on lactose, or on saccharose. Gelatin was not fluidified. The only atypical cultural reaction was that in the Hiss tube medium, where the very slight motility of the bacillus resulted, in early cultures, in close adherence to the stab, instead of general clouding. This, however, soon changed, the third, fourth, and subsequent transplants showing almost equal motility to the stock cultures. The agglutination reactions of this bacillus showed several points of interest. With the patient's blood this bacillus agglutinated in dilutions up to 1-300; whereas the patient's blood agglutinated a stock typhoid culture used for Widal reactions only 1-40. Agglutinated against typhoid immune serum and controlled by three laboratory strains of Bacillus typhosus, the bacillus from the patient agglutinated as highly as the others, the dilutions being carried to 1-1000.

It is not by any means clear exactly what this means. It seems to indicate that the blood of the patient had retained the specific agglutinin for this bacillus, but had, in the course of time, lost the group agglutinins for typhoid bacilli in general. This bacillus, on the other hand, had not lost those agglutinogens which rendered it subject to agglutination by a general typhoid immune serum.

Discussion.

Dr. L. Buerger asked whether the stools in this case had been examined for typhoid bacilli.

Dr. Zinsser said that they had not been examined, but that at the time of autopsy he had removed specimens from different

parts of the intestine from which cultures were made. In but nine was he able to find typhoid bacilli. He thought that the bacilli were probably there but were not demonstrated.

Dr. C. W. Field asked whether any absorption experiments had been done with the organism. It might not agglutinate either microscopically or macroscopically, and still absorb from the serum the specific agglutinins, though not showing any agglutinating action.

Dr. Zinsser said that he had not made such experiments.

Dr. James Ewing asked Dr. Zinsser whether he had tested the agglutinating effect of this patient's serum on any form of colon bacillus, especially on any colon which might have been found in the patient's intestine.

Dr. Zinsser said that he had not.

Dr. E. Libman asked whether the stricture of which Dr. Zinsser had spoken was complete. If it were, it might perhaps explain the absence of typhoid bacilli from the stools.

Dr. Zinsser said that the stricture was made complete by the small concretions in the duct which were pushed away by the probe.

RADIAL FIBRES IN ARTERIES (DUERCK).

ADELE OPPENHEIMER.

In *Virchow's Archiv* for July, 1907, Duerck reported that by means of Weigert's recent myelin-sheath stain he was able to demonstrate elastic fibres with exquisite distinctness and to show clearly that the elastic tissue system of arteries is not exactly what we have heretofore supposed it to be.

Recently Dr. A. E. Cohn sent Dr. Libman sections of arteries stained by means of Weigert's earlier myelin-sheath stain, which

aroused our interest. These were prepared in Professor Aschoff's laboratory.

There are under two of the microscopes to-night, cross sections of arteries stained (1) by Duerck's method and (2) by Dr. Cohn's method, that is with Weigert's earlier and later myelin-sheath stains.

Duerck's method as we have employed it is as follows:

1. Fix in Orth's formol-Mueller 24 to 72 hours.
2. Do not wash.
3. Imbed in paraffin or celloidin and cut thin sections.
4. Mordant with Weigert's neuroglia mordant for 24 hours.

This mordant consists of:

Chrome alum 2.5 parts.
Water 100.0.
Acetic acid (36%) 5.0.
Neutral copper acetate 5.0.

5. Wash briefly in 70% alcohol.

6. Stain with Weigert's iron hematoxylin stain which consists of solutions A and B, equal parts, mixed just before use:

A is 1% hematoxylin in 95% alcohol.

B consists of:

Ferric chloride fortis 4 c.c.
Hydrochloric acid 1 c.c.
Water up to 100 c.c.

7. After staining over night, wash in distilled water.

8. Differentiate in the following solution:

Potassium ferricyanide 2 parts
Borax 2.5 parts
Water 100 parts
} Diluted with three parts of water.

9. Wash in tap water, thoroughly.

10. Pass through three grades of alcohol, and through xylol, and mount in balsam.

Weigert's earlier myelin-sheath stain is very similar to this later one—it is also a cupric acetate-hematoxylin method, but simpler.

After treatment of sections according to these cupric acetate-hematoxylin methods, the elastic fibres stand out as if drawn with blue black ink on a tan background.

The sections stained according to the simpler method show in contradistinction to slides stained with orcein or with fuchsin-resorcin (1) many more fibres and (2) a well marked network. It is an open question whether this network is elastic or not.

The sections stained according to Duerck's method present an appearance very similar to those stained with orcein or fuchsin-resorcin.

In cross sections of medium sized and larger arteries, Duerck points out that there are seen in addition to the elastic elements between the muscle fibres, *many radical elements* stretching between these well-known circularly arranged elastic fibrils of the tunica media and binding them together. By means of these innumerable radial fibres, the elastica interna, the elastica externa, and the intermuscular elastic fibres of the mesial coat, and even the elastic elements of the adventitia of the arteries become one whole, are bound into one system.

Duerck is of the opinion that these elastic radial fibres dilate the vessels automatically. He suggests that the vessels are contracted after nerve stimulation of their circular muscles, then dilated automatically by the radial elastic fibres.

MYXOMA AND DIFFUSE HYPERPLASIA OF A FULL TERM PLACENTA.

JAMES EWING, M. D.

The specimen, for which I am indebted to Dr. W. M. Polk, was obtained from a patient who was delivered of a well formed infant at about term. The child lived only a few minutes. The pregnancy was uneventful, but unusual enlargement of the uterus had suggested the existence of twins. The placenta was delivered with some difficulty on account of its size. The organ measured 25 x 22 x 4 cm. There was a typical battledore insertion of the cord. Projecting from the fetal surface near the insertion of the cord was a rounded, firm, congested tumor, 16 x 8 x 4 cm. The lobules of the placenta throughout were very large, and the tissue was opaque, firm, light colored, and free from infarcts.

On section, the isolated tumor was composed of broad areas of myxomatous tissue interspersed with very numerous small villi. The spaces between the original villi were obliterated or compressed into narrow slits lined with flattened cells. The reddish color of the isolated tumor was due to retention of a moderate amount of blood in these narrow spaces. The cells of the myxomatous tissue were not very much increased in number except in certain foci, and the increase in bulk of the tissue was largely referable to increase of mucoid stroma. I was unable positively to identify mitotic figures. Throughout the remaining portions of the placenta, which was much increased in bulk, there was a pronounced increase in cells in and on the villi. Langhans' cells and syncytium were poorly differentiated, and the basement membrane separating Langhans' cells from the stroma of the villi was very faint or apparently absent. There was thus a diffuse hyperplasia of all stroma cells and lining epithelial cells of the villi throughout the placenta and this condition was responsible for the firm, opaque gross characters of the organ. The

exact significance of this change and its relation to the more definite localized myxoma, I am unable to explain.

The umbilical cord was of small diameter, and after hardening in formalin was of almost cartilaginous density. The vessels were tortuous. On section, no changes were found in the vessels of the cord, but the mucoid connective tissue contained an unusual admixture of collagenous fibrils, instead of the mucoid stroma.

Von Winckel states that about fifty tumors of the placenta of this general type are recorded. None of them proved malignant.

AN INTRAUTERINE PERITHELIOMA.

JAMES EWING, M. D.

This specimen, for which I am indebted to Dr. John Rogers, shows a very unusual structure among uterine tumors, and its exact nature I am unable to determine.

The patient, married, forty-eight years of age, had not menstruated since December, 1904 (three and one-half years). No history of abortion could be obtained. In January, 1908, irregular bleeding from the uterus began, sometimes profuse, with intervals of remission lasting a week. In March, a foul discharge began, and continued steadily, accompanied by frequent bleeding.

On admission to the hospital, the uterus was found enlarged, and tender; the os was patulous, discharging muco-pus; and a large tumor distended the cavity. The condition was regarded as a probable suppurating fibroid, while the suspicion of a malignant tumor was suggested by the spongy character of the mass. Hysterectomy was therefore performed, and was followed by prompt recovery.

Gross Examination.—The uterus measures 77x7 cm. On incision the uterine cavity was found to be occupied by a rounded, polypoid, solid tumor, measuring 10x6 cm., firmly ad-

herent over the anterior wall and projecting into and distending the cavity. The tumor was rather fragile, and on section was streaked with extensive areas of necrotic tissue. The uterine wall was thinned especially over the attachment of the tumor, and here the tumor edge was irregular, some nodules lying slightly within the muscularis; and along this portion necrotic areas were missing.

Microscopical Examination.—Fixation in 10 per cent. formalin. The outer half of the tumor was composed about equally of necrotic structureless material and masses of large polyhedral cells in advanced granular and hydropic degeneration. The deeper portions of the tumor are better nourished, supplied with a few delicate blood vessels, showing only occasional miliary foci of necrosis and composed of polyhedral cells in close apposition. These cells have well defined borders, clear or granular protoplasm and vesicular nuclei. In size they vary from 15 to 30 micra. Near the blood vessels the smaller cells predominate. Mitotic figures with well preserved spindles are very numerous, especially in the deeper portions near the muscularis. The growth of cells is nearly diffuse, no sinuses and no villi being found.

While a histological diagnosis of perithelioma is easily reached for this growth, yet the origin of the tumor is not clear. Three possibilities may be suggested. It is possible that the tumor arose from the stroma of the uterine mucosa, but I am not aware that any such tumors have been shown to take origin from such tissue. I was at first inclined to consider the possibility that the tumor was a true deciduoma; but no such growths have been observed from placental remnants, villi could not be traced in the tumor tissue, and the clinical history was against a recent pregnancy. Finally, it is possible that the tumor arose from an adrenal remnant, either primary in the uterus, or as a secondary growth after a primary tumor elsewhere of which no clinical signs were obtainable. The structure is distinctly that of hypernephroma. The future history of the patient may perhaps determine this point.

TYPHOID FEVER WITH MIXED INFECTION.

E. MOSCHCOWITZ, M. D.

Dr. E. Moschcowitz described a case of typhoid fever in which there had been a mixed infection with the Streptococcus pyogenes. The case was of interest for two reasons; first, because of the rare association of the typhoid bacillus and the streptococcus; and, second, because the pathological findings were not those ordinarily found in typhoid fever. The patient was a woman, fifty-two years of age, whose previous history was entirely negative. She first became ill on September 27, 1907. The symptoms complained of were intense headache, generalized pains, chilly feelings, and a slight fever. The temperature was 103°, pulse 110. Physical examination was entirely negative, with the exception of a few dry râles at the right base, which cleared up within a few days. The diagnosis of influenza was made, but despite the administration of appropriate remedies the temperature continued high. The Widal reaction was negative, and although taken every other day during the course of the next two weeks, remained negative. The temperature was of a very irregular type, and the pulse varied betwen 110 and 120; physical examination was still entirely negative. Nineteen days after she first became ill, a blood culture was taken and the report was "typhoid bacilli and streptococci." There were never any rose spots; the spleen was never palpable; or was there abdominal tenderness or distention. Antistreptococcus serum was injected twice, a few days apart, without any effect on the temperature or general condition. The opsonic index for typhoid bacilli was reported high; that for streptococcus, low. Symptoms and signs of hypostatic pneumonia developed a few days after the blood culture was taken, and these persisted until death. About four weeks after the onset a few clots of blood were passed per rectum, and the bowels, which previously had been constipated,

showed a tendency to diarrhea. The urine contained albumin throughout the last three weeks of the disease.

At the autopsy, the lungs showed intense congestion of both lower lobes; heart and liver were negative. The spleen was surprisingly small and hard; the mesenteric lymph nodes were not enlarged. The kidneys showed parenchymatous degeneration. The intestine showed ulcers, but not the kind seen in the fifth week of typhoid fever. These ulcers were sharply defined, having a "punched out" appearance. The edges were not raised. The bases of the ulcers were smooth and clean, and appeared to lie directly against the muscular coat. The ulcers ran in a transverse direction across the long axis of the gut. Over a few of the ulcers the peritoneum was slightly injected. Microscopical examination of the ulcers revealed nothing but what one might expect from the macroscopic appearance. No lymphoid tissue could be noted anywhere.

Dr. Moschcowitz felt that he could not account for the pathological findings; he thought that these findings could only be explained on the basis of one or two possibilities; either there was some maldevelopment of the lymphatic apparatus of the subject; or the association of the streptococcus had some effect in modifying the typhoidal lesions.

LESIONS IN A CASE OF MYASTHENIA GRAVIS.[1]

F. S. MANDLEBAUM, M. D. AND H. L. CELLER, M. D.

The specimens to be demonstrated were obtained from a case admitted in January 1907, to the Neurological Service of Dr. B. Sachs in Mt. Sinai Hospital. The history obtained from the patient, a Russian tailor, age 52 years, contained no facts of

(1) Abstract of article published in *The Journal of Experimental Medicine*, Vol. X, 1908.

etiological significance. The course of the disease, extending over a period of seven months, was marked by the characteristic symptoms of myasthenia gravis—progressive muscular weakness with short intervals of remission, the myasthenic reaction of Jolly, and sudden death with symptoms pointing to bulbar involvement. The autopsy, performed twenty-four hours after death by Dr. Libman, revealed no gross lesions of importance in any organ but the thymus. Occupying the site of this gland and generally conforming to its outline there was a tumor 5 cm. by 3 cm. by 2.5 cm., weighing 20 grams. On section the tumor appeared lobulated, firm, and pinkish-white in color and cells could be scraped easily from the surface.

Sections were cut from various parts of the tumor in order to determine its origin and relationship to the thymus gland proper. In only a few places could any normal thymus tissue be found. This, in some instances, was separated from the tumor by layers of connective-tissue, but in other places it was seen to be in direct relationship with the tumor. The thymus tissue has a normal appearance and contains a small number of Hassal's corpuscles, some of which show calcareous changes while others contain keratohyalin cells and polynuclear leucocytes. The tumor itself is separated from the surrounding structures by a well marked connective-tissue capsule and with the low power this is seen to extend into the tumor mass which is thus divided into numerous lobes.

Upon examination of the sections with the low power the tumor appears to be dotted with numerous slits, fissures and oval shaped openings. With a higher power it is seen that these openings are widely dilated lymph channels or lymph spaces lined with endothelium. The tumor proper is of a very dense cellular structure. The cells are quite large, of an oval, polygonal or irregular shape, and contain large vesicular nuclei with numerous chromatin granules. The cytoplasm is granular and stains lightly with eosin or picric acid. Throughout the sections the cells

have a tendency to form concentric bodies of fairly large size, somewhat resembling those found in psammoma and certain types of endothelioma, but having no direct connection with any blood vessels. As many as twelve, fifteen, or more, of these bodies may be counted in a single field. The cells in these concentric bodies are of spindle shape and their nuclei are long, narrow and curved as the result of compression. Some of the larger tumor cells contain two or more nuclei. A few cells show vacuolization of the cytoplasm, the nuclei remaining intact. A considerable number of nuclei throughout the sections show distinct nucleoli. None of the cells show any mitotic changes. A delicate stroma may be seen between the cells in those situations where the cells are less densely packed together. In some of the sections small islands of lymphoid cells are seen scattered between the tumor cells. No Hassall's corpuscles are found here, but these areas give the impression of being remnants of thymus tissue. Small masses of hyaline matter are seen here and there in the tumor, some of which are in close proximity to the blood vessels.

The lymph spaces are well filled with large spherical cells which show faint outlines and a coarsely granular cytoplasm. Most of the cells contain a small nucleus of irregular shape which is usually situated at the periphery. Besides these, smaller lymphocytic cells and granular matter are seen filling the spaces. Some of the larger cells show nuclear fragmentation. A few degenerated areas containing cholesterin crystals are seen.

The most interesting feature is the relationship of the tumor cells to the lymph spaces and blood vessels. All of the lymph spaces are lined by endothelial cells, as has been mentioned above. In some fields it appears as though several parallel layers of proliferated endothelium surrounded a considerable portion of the lymph space. These cells always stain more deeply than the tumor cells proper and in some situations form distinct bundles of spindle shaped cells merging gradually into the tumor cells. In other places the tumor cells appear to be

springing directly from the endothelium of the lymph spaces. This is most distinctly seen where the lymph spaces have been cut more or less transversely, and in such instances the cells have a slight tendency to grow radially from their walls.

Blood vessels are very numerous throughout the tumor. These consist principally of newly-formed capillaries, though small arteries with thin walls are also present. Some of the latter show well marked hyaline degeneration. A zone of lymphocytes surrounds each capillary. This may be seen in transverse as well as in longitudinal sections. In transverse sections these cells appear as a mantle in close relationship to the capillary wall. The anatomical position of these cells can be seen very clearly in longitudinal sections. Here we have a narrow band of cells on either side of the capillary and parallel to it. The cells are seen to be bounded on one side by the endothelium of the capillary and on the other side by a second row of endothelium which must be looked upon as the outer wall of the perivascular lymph space. In other words, these cells are confined to the perivascular lymph spaces. Just beyond these cells are clear spaces due to retraction or shrinkage and bounded by the tumor cells proper. The first layer of cells grows at right angles to the vessel walls and this radial arrangement may readily be seen with the low power. They also stain more intensely than those situated at a greater distance from the vessels. There seems to be no doubt that the tumor cells originally sprung from the endothelium of the perivascular lymph spaces, from which they have become detached. The endothelium of the capillaries is normal throughout and has no bearing on the formation of the tumor.

In this connection it might not be out of place to say a few words regarding the discussion which has arisen concerning the perithelium of blood vessels and its relationship to perivascular tumors. The perithelium of the blood vessels is supposed to represent the endothelium of the perivascular lymph spaces, but in most cases it is difficult or impossible to discover the presence of

a second layer of endothelium to form an outer wall of these lymph spaces. In the usual type of perithelial growth with a radial arrangement of the tumor cells these are always closely united to the vessel wall. This is not the case in our tumor, in which a well defined zone containing lymphocytic cells separates tumor cells from vessel wall. As far as the presence of any outer endothelial boundary is concerned, a study of our case demonstrates such a layer in those sections where the capillaries are cut longitudinally. The fact that a dilatation of all the lymph vessels with marked lymph stasis is present in our case may account for the comparatively easy recognition of the perivascular lymph spaces. It is possible that many of the recorded cases of perithelioma in which the cells appear to arise directly from the adventitia of the blood vessels and where the perivascular lymph spaces are not dilated, belong in this group. Our case demonstrates the fact that tumor cells may encircle and grow radially from a blood vessel and still have no direct attachment to the vessel wall proper, but arise from an outer layer of endothelium bounding the perivascular lymph spaces.

The proper classification of this tumor is somewhat difficult. Inasmuch as the growth is perilymphatic in character, it bears the same relationship to lymphangio-endothelioma as a perithelioma does to hemangio-endothelioma. It is therefore a perilymphatic lymphangio-endothelioma.

The lesion that may be considered characteristic of myasthenia was first recorded by Weigert in 1901. This consisted of cellular foci present in a number of the skeletal muscles as well as in the heart. Confirmatory observations have been recorded by a number of subsequent investigators although agreement is lacking as to the nature of the cells of which the foci are composed. In our case the infiltrations were found widely distributed throughout the voluntary muscular system.

A large number of sections from the psoas, longus colli, deltoid, supinator longus, rectus abdominis and diaphragm were

studied and the results were fairly uniform in every muscle. The constant lesion is the presence of smaller or larger areas of cellular infiltration. In all of the muscles examined we were able to find this lesion. In most instances these areas are seen without difficulty; at other times a long search is required. The cells in these infiltrations are of small size and uniformly round in shape. Their nuclei are relatively large, usually round or slightly oval in form, and stain intensely with hematoxylin and the nuclear aniline dyes. Morphologically these cells resemble small lymphocytes. No polynuclear leucocytes, plasma cells or eosinophile cells are present in the infiltrated areas, nor can any mitotic cells be seen. In sections where the muscle fibres are cut longitudinally these areas of lymphocytic infiltration are found to be situated between adjacent fibres. The infiltrations have a tendency, in longitudinal sections, to form long, narrow bands which are easily seen upon examination on account of their intense staining qualities. In transverse sections the cellular infiltrations are cut in the opposite axis and appear as oval or roundish areas which vary considerably in size. Some may show but 15 or 20 cells while others may present ten or twenty times that number. Buzzard has suggested the term "lymphorrhages" for these cellular infiltrations, coining the word to designate that they are composed of lymphocytic cells infiltrating the muscle fibres as do red blood cells in interstitial hemorrhages. Most of the transverse sections show from one to three small capillaries in the central part of each lymphorrhage. These capillaries appear quite normal and are often filled with blood. In the longitudinal sections it is more difficult to find these small vessels unless serial sections are examined. In the study of the deltoid several longitudinally cut capillaries are seen. It is possible, in some of these vessels, to see the perivascular lymph spaces with ease, on account of the presence of lymphoid cells which completely fill the dilated lymph spaces. In one of the capillaries the endothelium limiting the outer wall of the perivascular lymph

space is clearly seen. This condition is identical with that described in the thymic tumor. The muscle fibres in the immediate vicinity of the lymphorrhages show no degenerative or atrophic changes.

Some of the muscle bundles have a tendency to stain more intensely than others, but this is frequently seen in normal muscles and can not be considered as a pathological process. The striations are distinctly seen in all sections. In some of the muscles rather prominent bands of connective tissue may be seen. Some of these bands merge directly into the muscle fibres. At these situations the sarcolemma cells are increased in number and the transverse striations are somewhat indistinct. Some of these connective tissue bands have a more or less wavy outline and show a few indistinct oval nuclei. They bear a striking resemblance to muscle fibres in shape and size and must be looked upon as a replacement fibrosis, secondary to degenerative muscle changes. This lesion is most marked in the deltoid muscle. Otherwise only a normal amount of connective tissue is present. No evidence of fatty degeneration is seen in osmic acid preparations and no pigmentation can be found in any of the muscles. A few fibres are the seat of marked degenerative changes. This is particularly noted in transverse sections of the longus colli muscle. Here the fibres stain distinctly pinkish with Van Gieson's stain, and the muscle nuclei are increased in numbers. The protoplasm is somewhat granular, quite different from the homogeneous appearance noted in ordinary hyaline degeneration. This lesion as well as that described above as occurring in the deltoid may be considered as an early degenerative atrophic change.

In the study of the psoas muscle a few small areas are seen which show a different picture. Here the sarcolemma cells are very numerous but the muscle fibres apparently are unchanged. A few cells are also present showing pycnotic nuclear changes. It is difficult properly to classify these cells, but we look upon them as polynuclear leucocytes with degenerating nuclei.

Throughout the sections the walls of the blood vessels do not show any changes whatever. The medullated nerve fibres are likewise normal, and the sensory nerve-endings ("muscle-spindles") which are present in some of the muscles in large numbers are apparently free from any pathological changes.

After a long search through many sections it was possible to find a few small areas of infiltration in the tongue. Apart from their small size these areas do not differ from those found in the skeletal muscles. Otherwise no changes are present, either in the muscular portion, vessels or nerves.

The occurrence of lymphorrhages in the internal organs was first reported by Buzzard, who found them most constantly in the adrenals. In our case there was a large cellular infiltration in one adrenal, and numerous smaller ones scattered throughout the liver. In the foci in the latter organ the cells seem to be grouped in or about the capillaries lying btween the liver cells. It is to be noted that no degeneration of the parenchyma cells is present in the neighborhood of the lymphorrhages.

The published autopsies contain a description of many gross and microscopic lesions in the central nervous system, but the great diversity and inconstancy of these changes warrants the assumption that no pathological significance can be attached to them. Buzzard alone describes a cellular collection in a posterior root ganglion in one case of his series, that he regards as identical with those described in other tissues. In our case we have been able for the first time to demonstrate these foci in the central nervous system. A perivascular collection of lymphoid cells was present in the grey matter of the medulla near the tenth nucleus, and a number of smaller foci were found in the pyramidal tract central to the olivary body. The situation and scarcity of these lesions, however, leads us to believe that they bear no relation to the bulbar symptoms manifested clinically.

The origin of these cellular foci is still a moot question. By Weigert and by Blumer, in whose cases there was a lympho-

sarcoma of the thymus, they have been regarded as metastatic deposits. Their occurrence in cases in which no pathological condition of the thymus was present, as well as in our case, in which the thymic tumor was of endothelial nature incapable of producing lymphoid metastases, renders this theory untenable. More recently Marburg has advanced the hypothesis that myasthenia is a primary degenerative myositis, and holds the lymphoid infiltrations to be an inflammatory reaction. It has already been mentioned, however, that in our specimens the cellular foci bear no relations to the areas of muscle degeneration.

We have been able to collect from the literature forty-five cases of myasthenia gravis with more or less complete autopsy reports. It is noteworthy that in about one-fifth of this number some abnormality of the thymus, varying from simple persistence or hyperplasia to actual neoplasm, has been found. While it is manifestly impossible from these statistics to formulate a theory of the thymic origin of the disease, the relative frequency of changes in the thymus lends support to Weigert's suggestion that in a certain group of cases presenting the symptom-complex known as myasthenia gravis, the abnormally functionating thymus may play a causative role.

We are inclined to regard myasthenia gravis as a toxemia affecting not alone the muscles but all the other organs of the body as well. The influence of the thymus in producing this toxemia in a certain proportion of cases must be left an open question. A study of our specimens seems to warrant the conclusion that the lymphoid cells in the infiltrations present in the muscles and other organs are derived wholly from the dilated perivascular lymph-spaces and are an expression of the universal toxemia.

Discussion.

Dr. F. C. Wood spoke of a case of myasthenia gravis which he had recently seen at St. Luke's. Except that the thymus

was enlarged no lesions were found. There was not the slightest trace of any infiltration in the muscles or in any of the organs, so far as they had been able to determine. The thymus was approximately normal, though the germ centers were rather more developed than in an ordinary thymus. Hassall's bodies were abundant. The muscle showed no gross changes except atrophy, and it was still being sectioned in the hope that some infiltration might be found. The attempt was being made to get a satisfactory staining of the nerve endings in the muscle. Dr. Wood thought that the slight infiltration of the muscles in these cases did not account for the extreme weakness which the patients show.

Dr. James Ewing asked whether Dr. Celler regarded the origin of the tumor from the thymus as entirely proved. Such a tumor was not at all uncommon in lymph nodes, but he had never seen it in the thymus. Of course, the thymus being a lymphoid structure might give rise to such a tumor; but as the thymus was surrounded by lymph nodes it seemed to him that one must have very conclusive evidence indeed of the thymus origin before this could be claimed.

Dr. Horst Oertel asked whether the suprarenals showed any lesions in this case, and whether the chromaffinic system had been studied.

Dr. Celler, in answer to Dr. Wood, said that he had not meant to convey the impression that the lymphocytic infiltration was the cause of the muscular weakness. He had concluded that the disease was probably a toxemia of unknown origin which might, in some cases at least, arise from an abnormally functionating thymus gland. As regarded the origin of the tumor, while in some specimens uninvaded thymus tissue was preserved, in others a direct connection between the remains of thymus tissue and the tumor could be demonstrated. It seemed to him that if this were a tumor arising in the lymph nodes it would not have infiltrated the thymus alone, but would have invaded

other structures as well. In this case the thymus alone was involved. Furthermore, the tumor apparently occupied the central portion of the organ, whereas the areas of normal thymus tissue were found only at the periphery. The chromophilic system, as far as the adrenals only were concerned, was studied, but no changes were found.

TWO ATYPICAL KIDNEY TUMORS.

I. STRAUSS, M.D.

Dr. I. Strauss presented specimens of two atypical kidney tumors. The first was a kidney removed at operation by Dr. Ladinsky, which on examination proved to be a form of hypernephroma, showing marked cystic degeneration, and on section was of a glandular type. The tumor was sharply encapsulated. The condition of the adrenal was not ascertained. In many places it was difficult to determine the nature of the growth, but in certain parts it showed a typical perithelioma structure.

In a recent paper Stoerck pointed out that he was not able to find any evidence of a lumen in the adrenal in the human subject, and stated that he thought that the lumen reported in the adrenals of dogs and horses was due to a hemorrhage. In adrenals fixed in Orth's fluid the contents of the lumina were wanting, but when the organs were fixed in Zenker's solution there were present either evidences of blood or serum. He intimated that in the future he will side with those pathologists who consider this form of hypernephroma due, not to adrenal rests, but to some other form of growth.

The second case was a kidney also removed at operation. The patient had suffered from pyuria. In the pelvis of the kidney there was a calculus about 1 cm. in diameter. All these cavities

led down into the pelvis and their walls were necrotic. Streaks of firm yellow tissue were seen radiating out from these cavities and making a slight prominence under the capsules. When a section was taken of this part of the tumor it showed a structure very similar to a hypernephroma. The cells were vacuolated and their nuclei were in the center. They were arranged in rows and sometimes along the walls of a capillary. The cells did not react to osmic acid, but did to Sudan III.

Two pathologists had made a positive diagnosis of hypernephroma. Dr. Elser had called attention to the fact that at the New York Hospital he had had a case in which there was a tumor of the axilla. The surgeon had cut down on the supposed tumor and had sent specimens to the laboratory. On examination these same fat cells were found. Further examination proved the tumor to be due to gauze left in the axilla. These fatty cells might be a peculiar reaction of the fat to the stimulus of the foreign matter. It was possible that this tumor might be some of the pelvic fat which had undergone this peculiar degeneration, and grown out into the cortex, and that we had to deal with a simple pyonephroma. The tumor was full of lymph follicles showing typical structure of lymph gland. The specimen was stained for tubercle bacilli, but none was found.

Discussion.

Dr. C. W. Field asked Dr. Strauss whether any chemical analyses had been made to determine the relation between the cholesterin and the lecithin content of the cells. In these inflammatory conditions one should be able to detect the normal relationship between the various fats and determine their origin in this way.

Dr. Strauss said that such analyses had not been made.

Dr. F. C. Wood said in regard to the inflammatory case and also in regard to the tumor of the axilla which had been spoken

of, that one must always consider the possibility of such appearances being due to growing fat cells. In examining specimens of chronic inflammation from the broad ligament and pelvic tissues, he had noticed a large number of cells which looked like hypernephroma cells, but which on study proved to be regenerating fat cells. He had seen the same phenomena in other cases where hypernephroma could be excluded, for instance, in a case of adenoma of the breast. The bodies of the cells were granular or reticulated, and there were usually no discrete fat globules of any size in these cells. A chronically inflamed breast showed quite large multinuclear cells which had led to an erroneous diagnosis of giant cells and hence tuberculosis. The same was true of peritoneal inflammatory tissue. He had seen areas which looked so much like hypernephroma that one would consider them hypernephroma of the broad ligament. He thought it was not the custom to think of fat cells as anything but cells containing large quantities of fat, whereas these growing fat cells, for instance in the omentum, were very peculiar and looked very much like hypernephroma until they had collected their normal amount of fat. The same thing was found in the bone marrow in cases of osteomyelitis.

AGGLUTINATING ACTION OF RICIN ON ERYTHROCYTES IN ISOTONIC SUGAR SOLUTION.

C. W. FIELD, M.D.

Dr. Cyrus W. Field reported an interesting phenomenon which he had recently observed. Last year he had spoken to the Society of some work done in the past four or five years on the agglutinating reaction in bacteria, showing that the agglutinin reaction does not take place between dialyzed bacteria and dialyzed serum, but that electrolytes must be present.

In working with the red blood cells suspended in isotonic salt solution, there is naturally a large quantity of electrolyte present, and on the addition of ricin the cells are agglutinated. An interesting fact was that if the cells were washed in isotonic sugar solution three times and suspended in this mixture, and the ricin added, no agglutination took place, that is, if the agglutination tests were made immediately after the last washing. If the blood cells were allowed to stand for twenty-four hours or longer in the isotonic sugar solution, and the ricin then added, they agglutinated readily.

If to the isotonic sugar solution was added 1-10,000 normal sodium chloride solution, the agglutination took place immediately.

Without going into a discussion of the factors which brought about agglutination, Dr. Field said that he believed there was a passage of electrolyte through the envelope of the red cell into the surrounding fluid. This conclusion was practically opposed to all the work of Stewart, of Chicago, who as the result of his experiments has claimed that the envelope of the red cell is impermeable to the electrolytes. Nevertheless, Dr. Field believed that the phenomenon spoken of pointed very strongly to the fact that there was a passage of the electrolytes from the cells to the surrounding medium.

A REPORT ON MOUSE TUMORS.

J. W. JOBLING, M.D.

I wish to speak of certain results obtained during the last two years from the transplantation of mouse tumors. The results to be referred to were obtained with twenty-two tumors which had developed spontaneously in mice. The mice were pur-

chased chiefly from breeders. With the exception of three, all the tumors could be classified as adenocarcinomata, though one showed an almost solid growth of epithelial cells throughout the tumor.

Of the twenty-two tumors, three were obtained so recently that they are not included in the number developing when transplanted into other mice. Of the nineteen remaining, sixteen, or 84.2 per cent., developed tumors upon transplantation into other mice.

Seventeen of the tumors were composed of epithelial cells. They can be divided into two classes, namely, hemorrhagic and non-hemorrhagic. This division is made because some investigators claim that the hemorrhagic type of tumor is more difficult of successful transplantation. The incubation period—the time intervening between inoculation and appearance of tumor—was longer and the percentage of retrogressions greater, in our experience, than in those tumors which developed from the non-hemorrhagic precursors. In one series of ten hemorrhagic tumors, seven, or 70 per cent., were successfully transplanted, but of these, all the tumors in three strains underwent retrogression before they had become large enough to enable us to make further transplantations.

There were seven non-hemorrhagic tumors which were successfully transplanted into other mice, but all the tumors in two strains underwent retrogression in the first generation before they could be transplanted.

The average incubation period in the case of the hemorrhagic tumors was seventy-two days; of the non-hemorrhagic tumors seventy days. The longest incubation period noted was 150 days which occurred with two tumors, one being hemorrhagic and the other non-hemorrhagic. The average number of tumors developing in the first generation with the hemorrhagic tumors was 7 per cent., and with the non-hemorrhagic 9.5 per cent.

It has also been stated that but few of the mice with spontaneous tumors show lung metastases. Apolant reported that he found six examples of lung metastases in 221 mice.

Of our series, eight, or 42 per cent., of the nineteen cancer mice showed macroscopical lung metastases. Dividing these into two series as before, we have four, or 40 per cent., showing lung metastases in the hemorrhagic and four, or 44 per cent., in the non-hemorrhagic type. The tendency is about equal in both.

I wish now to speak of three mice, each of which had more than one tumor. The difficulty encountered in these cases in determining what should be called a metastasis, and what an original growth, is considerable. The first mouse exhibited a large tumor in the left inguinal region which was an adenocarcinoma, and a small flat nodule a little anterior to the right axiliary space, which was adenomatous in structure. The second mouse presented a large solid alveolar carcinoma in the right inguinal region and a second tumor in the lower lobe of the right lung—apparently identical with a tumor which Tyzzer has described as a papillary cystadenoma which he found in the lungs of two mice. The third mouse showed three tumors. The largest of the three was attached to the side of the neck and was hemorrhagic; the second was in the right inguinal region; the third, the smallest, was in the left inguinal region. Neither of the latter was hemorrhagic. Mice inoculated with material from the hemorrhagic tumor developed hemorrhagic tumors, while mice inoculated with material from the non-hemorrhagic tumor in the right inguinal region developed non-hemorrhagic tumors.

Finally, I wish to refer to three mice, two of which presented tumors composed of lymphoid tissue and one a tumor of a spindle cell sarcomatous nature. The first of these was a mouse showing general hyperplasia of the lymphoid tissue. In the neck there were two large masses each measuring about 1.5 cm. in diameter; in both axilliary regions, masses measuring 7

mm. and in addition masses in the left inguinal region, mesentery and retroperitoneal tissues. The condition resembled the so-called malignant lymphoma of Haaland. Haaland reported six instances, but in no case did he obtain any growth in other mice inoculated with the tumor material. But he states that, after placing normal mice in the cage with a mouse having lymphoma, five similar tumors appeared within two years. With the material from the mouse mentioned, I inoculated 100 mice and, up to the present time, one of these has developed a tumor which, histologically, is identical with that used for inoculation.

The second mouse also had a tumor of lymphoid structure. In this mouse there was no general hyperplasia of lymphoid tissues. It is too soon to say if tumors will develop in mice inoculated from this tumor.

The last mouse, presenting a spindle cell sarcoma on the left side of the chest, has come into my hands so recently that no report can yet be made upon the results of its transplantation.

Discussion.

Dr. Charles Norris said that from an examination of the mouse with the axillary tumor and the lung tumor, it certainly seemed as though there were two different tumors. He had been much interested in the general lymphosarcoma of the mouse, and thought that that line of tumors would be the most fruitful as far as etiology was concerned.

A CASE OF TUBERCULOSIS IN A CAT.

A. F. HESS, M.D.

Dr. A. F. Hess showed a case of tuberculosis in a cat which had been sent to the Department of Health laboratory to be examined for rabies. No Negri bodies could be found, but the

autopsy disclosed marked tuberculosis of both lungs with enlargement of the mesenteric glands. There were no lesions in the intestine and stomach, and the only other lesions were marked petechial hemorrhages throughout, in the kidney, mesentery, pleura, and meninges.

The history showed that the cat had been in the family for three months; it had not been well and was considered lazy. It had been fed on raw milk as well as other things. There were no tuberculous individuals living in the house. The only symptom pointing to the involvement of the lungs was a cough which the cat had had for some time.

On looking up the literature, Dr. Hess had found that Abel of Leipzig had made autopsies on cats sent to him with symptoms suggesting tuberculosis, and that among four hundred cats he found nine cases of tuberculosis. The only case Dr. Hess had found in which the bacillus was isolated, differentiated, and cultivated, was one where the human type of bacillus was found.

NOTES ON BLOOD CULTURES IN HUMAN GLANDERS.

BURRILL B. CROHN, M.D.

The following notes on blood cultures in human glanders have been collected after a fairly complete search through the literature on that subject, and include the data obtained from a case which was admitted to Mt. Sinai Hospital in August, 1907.

In regard to blood cultures in glanders the literature is rather meagre in cases in which this diagnostic aid has been utilized. Most of the cases have been studied very completely from the clinical and also the pathological standpoint, but in only a few cases has an attempt been made to cultivate the Bacillus mallei

from the blood. I have collected fourteen reported cases of glanders or farcy; our own case not yet in the literature, makes the fifteenth. These cases are divided clinically, on the basis of duration of the illness, into acute and chronic glanders or farcy. (It should be noted that the clinical subdivision of this disease into two classes, namely glanders and farcy may be disregarded in this paper as all the cases under discussion have shown practically only one picture, namely a combination of the type called farcy with that of glanders, the former predominating throughout the course.) The clinical histories in these cases correspond very closely. There is almost invariably a history of exposure to glandered horses. In four of the cases there was an actual point of inoculation on the hand; the onset was acute with sharp pain in the lower thorax, fever, chills, malaise, general prostration. Initial symptoms referable to the lungs is the rule in over 80 per cent. of the cases. The picture of a general pyemia supervenes rapidly, or is present from the beginning; numerous subcutaneous and intramuscular abscesses form, followed later by a pustular rash; there is increased prostration, rapidly developing delirium or coma, and death in from ten to thirty-six days. The picture is invariably one of a profound pyemia and toxemia with early or late lung involvement. The localization of the infection in the upper respiratory passages, so characteristic of glanders in the horse is rarely seen in man, in whom the picture of a farcy, that is accentuation of the localized point of inoculation with rapidly developing blood invasion and the establishment of metastatic foci in the muscles and joints predominates.

Of the fifteen cases under discussion to-night there are thirteen acute and two chronic cases. Of the thirteen acute cases ten gave positive blood cultures. Of the three cases of acute glanders in which the organism was not recovered from the blood, one case reported by Woodcock should be disregarded as the subsequent bacteriology of the whole case was not satisfac-

torily nor conclusively worked out; nor was the organism from the lesions proved beyond a doubt. Of the ten positive cases, the blood culture was obtained when the disease was well advanced in its course. The earliest culture taken in our own case was on the seventh day of the disease, the total course being only eleven days; the remainder of the cultures in the series were taken from one to four days before death. In all but one of the cases there were already established numerous metastatic abscesses and active lung signs; in six out of the ten the pustular rash had already made its appearance. In all the cases at the time of culture, there was marked prostration, high continuous fever, rapid pulse, and other signs of an intense infection.

Looking over the two cases of acute glanders with negative results as to blood cultures (omitting from the discussion Woodcock's case), it is noted that these cases correspond in their clinical picture fairly accurately with those in the previous series of positive results, the only difference being in a somewhat longer duration of the disease, and a less rapid appearance of the local pyemic foci. In these two cases the attempt to isolate the organism from the blood was made earlier in the course of the disease than in the previous series; in the first case, Gutowski's, on the 13th day (total duration 27 days); in the second, Potter's case, on the 21st day (total course 35 days); in neither case was the generalized pustular rash evident at the time of the blood culture. The case reported by Van Ingen is of special interest for the reason that two blood cultures taken respectively on the 23rd and 25th day of the disease were negative, though lung involvement and numerous metastatic abscesses were present. A blood culture taken on the 30th day, two days before death, and the day just preceding the appearance of the pustular rash, was positive.

Of the two chronic cases, both with negative blood cultures, that of Post had run a course of nine months with lung and

metastatic foci but no pustular rash. (The patient was still living at time of publication of his paper.) That of Sieur ran a course of two and a half years following a local infection of the finger and presented the symptoms of a chronic pyemia without lung or cutaneous signs except toward the very end.

Conclusions.

The deductions to be drawn from a study of those cases of human glanders with blood cultures is as follows: In acute cases, cultivations from the blood early in the course of the disease are likely to be negative. Those taken later in the course, particularly at the time of and after the appearance of the pustular rash, are invariably positive; chronic cases give negative results. These conclusions are singularly in contrast with the results obtained by workers in the field of equine glanders. MacFadyean, an eminent authority on this subject, writing in the *Glasgow Journal of Comparative Pathology and Therapeutics,* says: "The glanders bacillus is a tissue parasite and in all cases of glanders in the horse it is almost entirely confined to the lesions and the discharges from them. It is no doubt transported by the blood as well as lymph channels, but the disease in the horse is never septicemic. Even in the acute case the bacilli are so sparingly present in the blood that their discovery by microscopic and cultural methods is nearly always impossible, and even considerable quantities of blood fail to transmit the disease by inoculation."

The explanation of this apparent inconsistency is, that the disease in the horse rarely, if ever, runs so acute a course as it does in man, manifesting itself mainly as a subacute or chronic affection of the respiratory apparatus or as a localized farcy of the skin and related lymph organs. The corresponding type in man that of the so-called chronic glanders, gives, as we have seen, similarly negative blood cultures. The usual picture in

man, however, is that of a rapidly developing and grave pyemia with a less considerable and slower involvement of the related lymphoid apparatus, but with the rapid development of metastatic muscle, bone and joint foci which can only have been transmitted by the blood current. It is quite probable that the bacteria are present in the blood in human cases early in the disease, in fact, as early as the first metastatic deposit makes its appearance, but probably they are in such few numbers that our present methods are incapable of demonstrating them. It is in the later stages of the disease when the bacteria become much more numerous in the blood (as evidenced by the outbreak of a general pustular rash, the pustules containing the bacilli), that we are successful in cultivating them from the blood. In the chronic cases, those which present the picture of localized glanders of the respiratory tract, the blood is probably sterile; in those cases with the establishment of farcy buds and metastatic foci, it would perhaps be possible to cultivate the organisms from the blood if the attempt were made just at the time of the new outbreak; between the recurrences of localized depositions peripherally, attempts at isolating the specific organism from the blood would probably be unsuccessful.

As to the nature of the bacillemia the same question arises here as arises in the discussion of the mode of infection of the blood current in typhoid fever. Is it a true bacteremia or is it an overflow? In speaking of typhoid, Coleman and Buxton think that the bacillemia is secondary to the infection of the lymphoid apparatus of the gastro-intestinal tract and is an overflow from the lympho-poetic system. Whether the infection of the blood stream in glanders is analogously the result of an overflow from the lymphatic involvement which invariably accompanies the local lesion is one view; if we accept the hypothesis of the possibility of a primary infection of the lungs and respiratory tract by inhalation, we must suppose the bronchial glands to be the source of overflow in most of our cases.

On the other hand, the recent work of Duval on "Vascular Lesions in Experimental Glanders" shows that there is a marked reaction of the vessel wall to the specific toxin, and that thrombosis of the vessels in the neighborhood of the point of inoculation occurs. In the light of these facts it may be supposed that the metastatic foci and free bacteria have a common origin in these thrombi, and that the metastatic deposits result from minute thrombotic emboli, although it must be stated that true infarcts or secondary foci in those organs in which they usually are found have not been demonstrated in glanders. A third view, that it is a true bacteremia, may be considered, since in our case the second blood culture taken two days after the first showed an increase in the number of bacilli present. We must suppose on this hypothesis that human glanders is a bacteremia the source of which is usually the lungs or respiratory tract, and in which the circulating bacilli establish by preference pyemic foci in the muscles and joints.

Prognosis.—Unfortunately the prognosis as judged by positive blood culture, is about the same as that held for the appearance of a pustular rash; that is, fatal.

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Dr. E. Libman, *President.*

TWO INTERESTING TYPES OF BONE SARCOMA.

LEO BUERGER, M. D.

The two specimens which I am about to present to you are of interest both to the pathologist and to the clinician. They show rather unusual types of myelogenous sarcoma, one developing in the upper end of the tibia, the other in the lower part of the femur. Most of the myelogenous sarcomas of the long bones are of the soft variety, and are often vascular and hemorrhagic, sometimes the seat of cystic or hemorrhagic softening, and usually attended by expansion of the bony cortex.

The two tumors to which I wish to call attention, belong to the *osteoid sarcomas,* one being almost of the pure osteoid variety, the other combining a fibro-sarcoma with the osteoid type of growth. Both of these present certain features in common: they have grown diffusely in the spongy bone without showing any tendency to disintegration; they are the site of marked calcification and ossification; expansion of the bony cortex is absent; and, in both cases, after producing extensive change in the interior of the bone itself without causing visible external manifestations, the tumors have perforated the cortex of the bone and produced fairly large rapidly growing extra-osseous tumors.

The first specimen, an osteoid sarcoma of the tibia, was taken from a boy of seventeen, operated on by Dr. Gerster of Mt. Sinai Hospital. There was a history of a slight sprain three months previous to amputation, but the tumefaction in the neighborhood of the knee was observed for only about a week.

Description of the tumor:—The upper and outer aspect of the leg in its upper fourth is occupied by an ovoid swelling. In this region there is an exploratory incision, the fascia muscles have been cut and in the depth of the wound soft, bloody tumor tissue is found. The muscles of the leg over the tumor are slightly thin and stretched, and somewhat edematous; and the deeper layers show beginning infiltration by soft grayish (probably tumor) tissue. Occupying the external surface of the tibia and traversing the shaft at one place so as to cause slight tumefaction posteriorly, there is an ovoid sessile tumor extending from the epiphyseal line downward for about four inches. At the middle of this mass the growth is thickest, about one and one-half inches. Upon section of the tibia we see that the tumor may be divided into a periosteal and a medullary portion. The periosteal consists in the main of a calcific or bony mass which forms a large part of the extra-osseous tumor and which can be traced through the thinned out remnants of the cortex into a similar sclerotic or calcific tumor in the head of the tibia.

Capping this hard periosteal tumor, is the soft infiltrating and partly disintegrated ovoid mass previously described. The medullary part of the tumor is also for the most part stony hard in consistency, infiltrates the whole of the upper end of the diaphysis, and shows no evidences of soft tumor tissue until a point in the shaft about five inches below the epiphyseal line. Here, although still retaining a slightly osseous nature, the sclerotic tissue seems to be mixed with softer elements which give it the appearance of true tumor. The tumor ends abruptly at a point just below the middle of the shaft. We have here then a new growth which has probably originated somewhere in the upper end of the diaphysis, and which has diffusely infiltrated the cancellous bone and has been almost completely converted into a hard stony mass. Although its relation to the extra-osseous growth is not perfectly clear at all points, it is fair to assume that perforation of the cortex had occurred in a number of places and that a growth was produced which possessed the tendency to sclerosis which was characteristic of the primary growth. Having attained certain dimensions, the character of the tumor tissue suddenly became altered and rapid proliferation around the tibia took place causing a large soft typical sarcoma mass.

Microscopically we may divide the tumor into two parts, the hard and the soft portions. The soft portions show rather typical osteoid sarcoma with a predominance of the cellular elements and in places large collections of giant cells. Here and there islands of atypical cartilage formation can be observed. The sclerotic parts show a diffuse calcification either of well defined masses of osteoid ground substance or diffuse deposits of calcium salts poorly differentiated in the cellular substance.

From the standpoint of the pathologist, the specimen, therefore, is of interest because it shows the sudden change of a calcifying, osteoid growth poor in cells, a tumor of slight malignancy, into a rapidly growing soft cellular variety, in which the histological picture is quite different from that found in the main tumor mass. When reporting to the surgeon, therefore,

on excised portions of soft extra-osseous sarcomas, we must bear in mind that whenever osteoid or cartilaginous tissue is present, there may be a calcifying or ossifying diffuse tumor growth in the bone itself.

Clinically, sclerosing tumors of this type are of interest because they might be diagnosticated by the X-ray picture long before the alteration into soft variety occurs, and before marked external deformity is present.

In the second specimen the difference between the character of the extra-osseous and the medullary growth is even more striking. Here in a large tumor of the lower end of the femur, the sections removed for diagnosis from the soft parts were of the osteoid and chondroid sarcoma variety, and we were rather surprised to find that practically the whole of the myelogenous growth belonged to the fibro-sarcoma type.

Description of the tumor:—Occupying the anterior and inner aspect of the lower end of the femur there is an ovoid tumor about the size of a large fist, its most prominent part corresponding to a point just above the internal condyle. In front, it extends completely across the femur, and upward for about two inches above the articular surface. In this situation, the tumor is one and one-half inches thick, and pearly and gritty on section, and can be traced directly into the medullary cavity through an irregular opening one cm. above the articular surface. On the internal aspect the tumor has been incised and shows evidences of disintegration and hemorrhage. Here it is made up of a number of lobulated nodules disposed around a stalk of dense osseous tissue which has its base at the adductor tubercle and which is part of the diffuse ossifying process that occupies the adjacent portions of the shaft and lower end of the bone. On section of the bone we find that the cancellous tissue is everywhere infiltrated by tumor of cartilaginous consistency. Although the cortex is somewhat thinned in places, there is no expansion. Perforation of the cortex has occurred in a number of places, the largest being anteriorly, from which point the extra-osseous tumor has probably originated. In the inter-

condylar notch the tumor has caused a prolapse of the synovial membrane, but has not as yet entered the cavity of the joint. The shaft of the femur is also infiltrated and the upper end of the tumor can be easily separated from the normal marrow by a zone or hemorrhage five inches above the intercondyloid notch.

Here too then we have a diffusely growing tumor starting in the end of one of the long bones, producing a diffuse infiltration of the cancellous tissue and shaft, becoming partly ossified and calcified, manifesting this tendency in part of the extra-osseous growth, and finally changing its character into a rapidly growing soft variety.

Microscopically the medullary portion shows fibro-sarcoma, the production of fibrous intercellular substance preponderating except in those places where the tumor has recently perforated the cortex and shows evidences of rapid growth. A part of the extra-osseus growth is calcified but in the main it presents a new picture, namely, a combination of osteoid sarcoma and chondroid sarcoma with areas in which the predominance of the cellular elements are of so striking a feature that the osteoid tissue is difficult to find.

The two tumors, then, resemble each other in the presence of osteoid portions, in the tendency to sclerosis, in the absence of expansion of the bone, and in the transformation of type occurring in the extra-osseous growth. Here, too, a diagnosis by means of the X-ray could probably have been made long before there were any external signs.

I have brought with me another specimen of osteoid sarcoma because it shows quite a different development. Here you see a small soft growth in the lower end of the femur, which soon penetrated the bone and produced a large mass in the soft parts. This was evidently a rather malignant type in which the absence of calcifying and ossifying changes may be held accountable for the rapidity of its advance.

BONE FORMATION IN THE KIDNEY AFTER PARTIAL EXTIRPATION.

RICHARD M. PEARCE, M. D.

Dr. Richard M. Pearce showed some sections illustrating heteroplastic bone formation in the kidneys of dogs. The condition was found in the course of some experiments which had for their object the reduction of the kidney of the dog to a minimum compatible with life. The injury consisted of a transverse bisection of the kidney; the new bone was found in the newly formed tissue resulting from this injury. It occurred in six kidneys in a series of fourteen dogs, after periods, respectively, of twenty-two, thirty-three, thirty-five, forty-eight (2), and 164 days. The facts to which Dr. Pearce wished to draw attention were, in the first place, that with the exception of the rabbit's kidney, heteroplastic bone formation had not been observed in the kidney of any animal. There were no records in the literature of its appearance in the kidney of man. There were four observations concerning bone formation in the rabbit's kidney after ligation of the renal vessels (Sacerdotti and Frattin, Poscharisskey, Maximow, Liek). These experiments were based on Litten's well known observation that ligation of the renal vessels is followed by necrosis and calcification of the kidney substance with the ingrowth of granulation tissue from the capsule. Calcification and granulation tissue appear to be the important factors in new bone formation, and this was obtained by the observers quoted in about 60 per cent. of their animals.

Liek had attempted to produce the same condition in cats, but without success. He commented on the fact that this bone formation in the kidney had been found in no animal except the rabbit and offered as a possible explanation the low calcium content of the blood of most animals as compared to that of the rabbit, the percentage being 1.62 for the rabbit, against 0.077 for the dog. The observation of the occurrence of bone formation in the dog's kidney, here presented, did not support Liek's explanation.

Another point was the occurrence of bone in the simple repair of the slight necrosis following partial extirpation, as contrasted with its occurrence in the repair of diffuse necrosis following ligation.

A third point was the type of ossification, that is, the formation of bone directly in connective tissue without evidence of previous deposition of lime salts.

An important point also was the occurrence, in each of the six kidneys, of the new bone immediately under the pelvic mucosa and nowhere else. For this localization no explanation could be offered.

The literature on the general subject of heteroplastic bone formation had recently been well covered by the papers of Bunting and Buerger and Oppenheimer.

A SIMPLE METHOD OF PERFORMING SERUM REACTIONS.

ALBERT A. EPSTEIN, M. D., AND REUBEN OTTENBERG, M. D.

Dr. Reuben Ottenberg presented for Dr. Epstein and himself a simple method for performing serum reactions, and added a few remarks on some interesting results which had been obtained.

The method arose in the first place from the necessity of testing for hemolysis in cases in which transfusion of blood was proposed. Since the work of Drs. Beebe and Weil on the hemolytic effects of malignant tumors, since Crile's report of very frequent hemolysis by sera of cancer patients, and since Pepper's report of a fatal case of hemolysis following transfusion, it has been well recognized that hemolysis, though not common, does occur on mixing human bloods. Pathologists are now called upon to examine the blood of persons on whom a transfusion is to be performed. To do this test it has usually been necessary

to secure several cubic centimeters of blood. In practice, however, it has often been impossible to do this, either on account of the urgency of the case, or of the fact that the patient was an infant. For this reason, the present method, which is practically an application of Wright's opsonic technique, has been evolved. The method requires but a few drops of blood, and can be carried out very quickly.

The things required are:

1. Glass capsules made of small caliber tubing (4 to 5 mm. in diameter) drawn out at both ends into fine capillaries.

2. Pipettes made of glass tubing (6 to 8 mm. in diameter). These are fitted with nipples.

3. Pipettes like the above but made of tubing of 4 to 5 mm. in diameter.

4. Normal salt solution (0.85 per cent.) to which 1 per cent. of sodium citrate has been added.

In obtaining the blood, the lobule of the ear is pricked with a needle. To prepare the suspension of red blood cells, the blood which oozes out is drawn up to an arbitrary mark on the first stem of one of the larger pipettes. This blood is then diluted by drawing into the same pipette successive portions of the salt-citrate solution up to the mark, allowing a small bubble of air to intervene between the portions. The blood can thus be diluted to any desired extent; usually a 1-10 dilution is used. After the blood and the citrate solution have been thoroughly mixed by running the two up and down in the pipette, the tip of the pipette is sealed in the flame. If desired, this pipette can then be used as a centrifuge tube and the blood cells washed in salt solution until free of serum. In practical tests before transfusion, however, this is not necessary, as after transfusion itself both sera are present in the vessels of the recipient.

The serum for the test is obtained by immersing the tip of the glass capsule in the issuing drops of blood. The capsule fills itself by capillary action. When the capsule is about three-quarters full, its free end is sealed in the flame. The capsule is then centrifuged, and clear serum is obtained in a few minutes.

(To make the test even more practical, so that it can be carried out at the bedside, Dr. Epstein has devised a small portable hand centrifuge.)

To carry out the test, equal volumes of serum and red blood cell suspension are mixed in the smaller pipettes described above; the capillary ends of the pipettes are sealed; and the mixture is then incubated at 37.5° C. for one to two hours. Observations are then made.

Of the ninety cases tested up to the present the results so far as hemolysis is concerned will be presented in a future communication.

One thing, however, seems to deserve discussion here; namely, the possible role of agglutination in transfusion. Up to the present, this point, though mentioned by Hektoen, has not received sufficient consideration. The reaction of agglutination is so striking as to lead to the thought that agglutination might be a danger in transfusion. Though there is no conclusive evidence on the subject, this might account for some of the unfavorable results in transfusion. Dr. Pearce has shown in experiments on dogs, that the injection of agglutinative sera causes severe symptoms and frequently death, due to thrombi of agglutinated red blood cells in the liver. Whether or not this is a real danger in transfusion remains to be settled by further investigation.

Tabulation of the agglutinations was begun simply to find out whether the results of the tests were reliable and would coincide with those of other observers. The beautiful way in which the bloods of various persons arranged themselves in sharply defined groups was very striking.

It was first pointed out by Landsteiner, and later by Hektoen, Gay, and others, that according to the mutual agglutinations of their sera, bloods could be divided into three classes, defined as follows:

1. In the first group the red blood cells are not agglutinable by any other blood, although the serum is found to agglutinate the red blood cells of all persons not of this group.

2. The second group is agglutinated by the first and third groups, but it agglutinates only the third group.

3. The third group is agglutinated by the first and second; but it agglutinates only the second group; occasionally also members of the third group.

This grouping was remarkably regular. Out of all the tests there was really not one blood which did not fit into it. There was one exception in which with repeated trials the red blood cells of group 2 were not agglutinated by the serum of a blood which clearly belonged to group 1, since it was not agglutinated by any other blood.

The explanation of this grouping is very much in dispute, and several theories have been put forward. Gay has tried to prove that the grouping is due to differences in tonicity of the serum. Hektoen, on the other hand, believes that there are different specific agglutinating substances, and that a given blood may possess one or two or none of them. His view, which seems the more reasonable, is supported by his absorption experiments, in which after the agglutinating power of a serum for the red blood cells of one class had been absorbed by an excess of red blood of that class, the serum still retained its agglutinating power for red blood cells of another class.

The coincidence of a brother and sister, whose bloods were examined, belonging to the same agglutination group, led the authors to inquire whether this blood characteristic, which from the work of Hektoen and Gay seems to be a permanent characteristic of the indivdual, is hereditary. Hektoen tested a family, and found that the mother and three of the children belonged to group 1, and the remaining child to group 2. The authors tested two families. In the one the mother and seven children were all found to belong to group 2; the father could not be examined. In another family, mother, father, and four children all belonged to group 3. It seemed probably a coincidence that the father and mother were of the same group, but possibly a matter of heredity that the children were.

Before any definite conclusions can be reached on this point

AGGLUTINATIONS

RED BLOOD CELLS

SERA		I							II				III			
		52	53	54	55	56	57	45	46	42	43	50	47	48	49	
I	52	—	—	—	—	—	—	—	+	+	+	+	+	+	+	Second Family
	53	—	—	—	—	—	—	—	+	+	+	+	+	+	+	
	54	—	—	—	—	—	—	—	+	+	+	+	+	+	+	
	55	—	—	—	—	—	—	—	+	+	+	+	+	+	+	
	56	—	—	—	—	—	—	—	+	+	+	+	+	+	+	
	57	—	—	—	—	—	—	—	+	+	+	+	+	+	+	
	45	—	—	—	—	—	—	—	—	—	—	—	+	+	+	
II	46	—	—	—	—	—	—	—	—	—	—	—	+	+	+	
	42	—	—	—	—	—	—	—	—	—	—	—	+	+	+	Brother and Sister
	43	—	—	—	—	—	—	—	—	—	—	—	+	+	+	
	50	—	—	—	—	—	—	—	—	—	—	—	+	+	+	
III	47	—	—	—	—	—	—	—	+	+	+	+	—	—	+	
	48	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
	49	—	—	—	—	—	—	—	—	—	—	—	—	—	—	

AGGLUTINATIONS

SERA	RED BLOOD CELLS: I						II First Family													
	25	26	28	30	31	34	27	29	32	33	35	36	37	38	39	40	41	42	43	44
25	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
26	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
28	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
30	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
31	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
34	—	—	—	—	—	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
27	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
29	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
32	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
33	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
35	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
36	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
37	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
38	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
39	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
40	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
41	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
42	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
43	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
44	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—

I

II

First Family

a great deal of careful work must be done, and the authors hope to present further studies later on. It seems, however, from the sharply opposed nature of these blood characteristics that if they are inherited at all they will form a very good example of the Mendelian law of heredity.

Discussion.

Dr. S. P. Beebe asked whether or not it had been possible by the use of this method to detect any dangerous elements in transfusion and prevent dangerous transfusions; or whether any transfusion had been made in a case where this test showed hemolysis to exist, and if so, what results had followed.

Dr. Ottenberg said that they had not yet been able to use this method in any cases which had been followed by transfusion. They had been working on it for only three weeks. Before that the tests were done in the ordinary way. In one case in which hemolysis was detected the proposed transfusion was not done. Dr. Ottenberg said that he knew of one case in which slight hemolysis was detected, and yet the transfusion was done. It was followed by some hemoglobinuria, etc., but nothing serious resulted. Evidently hemolysis was not always a contraindication. Nevertheless tests should always be made and a marked hemolysis should be regarded as a distinct contraindication to transfusion.

THEORETICAL AND PRACTICAL CONSIDERATIONS CONCERNING THE SIGNIFICANCE OF THE CONJUNCTIVAL REACTION (OPHTHALMO-TUBERCULIN TEST).*

A. WOLFF-EISNER, M. D.

The new tuberculin reactions have opened up a wide field in connection with both theory and practice and have revived the discussion of many questions that had come to a standstill. I do not regard it as my task this evening to take up all of the theoretical questions; and the lack of time would preclude this. I shall occasionally refer to the papers in which those interested may find future data that may interest them. I believe it would be best to pick out a few practical questions and try to come to a conclusion concerning them.

Recently a number of new tuberculin reactions have been placed at our disposal for the diagnosis of tuberculosis. A large amount of literature has followed the first publication about these matters, a great part of which is worthless because of an insufficient knowledge of the fundamental basis of the reactions on the part of the observers. A recital of such examples is not in place. Such publications have caused confusion and dispute, a fact which has made the practitioner avoid this field of contest. But the time of toil and trouble will pass. It was the unavoidable result of an unsubstantiated approval of methods, from which I kept aloof, as is shown in my first communication on the subject. We have now first the old subcutaneous method of Koch; second, "the Stichreaction," though just as old, newly applied; third, the "cutaneous" and the conjunctival reaction; fourth, a series of so-called new reactions which I will not discuss.

The subcutaneous reaction is a specific one; it is a very sensitive test. A positive result indicates the presence of tuber-

*Read by invitation at the meeting of the New York Pathological Society on October 14, 1908.

culosis, but does not demonstrate necessarily an active or clinically evident tuberculosis. The occurrence of a positive reaction in 50 to 80 per cent. of clinically healthy individuals tested by the subcutaneous method should guard against such an error. I would not mention such a self-evident fact before this assemblage were it not that such errors are made daily in practice and stated in literature.

On the whole, the cutaneous and the "Stichreaction" give the same results as the subcutaneous method, which fact establishes their importance for clinical purposes. They are simple, safe methods which can be substituted for the subcutaneous method, demonstrating the same facts. They demonstrate a tuberculous focus which, however, may be inactive or latent.

The conjunctival reaction differs materially from the "cutaneous" and the Stichreaction, being a reaction on a mucous membrane. It is positive in active tuberculous processes which are not too far advanced and does not react in those cases in which a clinical examination is negative. It has already been shown that some of the apparently healthy people who gave the reaction had active tuberculosis. The future will tell whether or not tuberculosis is present in the remaining 5 to 8 per cent. But we can say to-day that, in contradistinction to the other tuberculin reactions, the conjunctival reaction is the one which indicates an active tuberculosis. An apparently healthy individual showing a positive conjunctival reaction is to be regarded in a suspicious light as being afflicted with an active tuberculosis.

These facts are proven by the records of reaction in 4,000 cases obtained under all precautions. The diagnostic value can only be found in the positive reaction. I have never stated that the negative conjunctival reaction excludes the presence of active tuberculosis, but it is improbable, excepting in cases in which clinically an active tuberculosis is present. For this reason the conjunctival reaction has a greater diagnostic value than the subcutaneous reaction. At first we considered them of equal value, but comparative examinations in about 100 cases have

convinced us of the greater clinical value of the conjunctival reaction.

The inherent difference between the tuberculin local reaction and the subcutaneous method lies in the production of a typical tuberculin reaction far from the seat of the existing disease, that is, the avoidance of lighting up a fresh process at the seat of the original lesion. The rise of temperature in the subcutaneous method is not the element of danger, but the starting up of activity at the seat of the old lesion is the serious consequence; a process, the progress of which can not be limited. In the recognition of this specific advantage of the conjunctival reaction, the contraindications become evident, which I have adherred to from the beginning, having neglected them only once, in consequence of an error. In a paper read before the Berlin Ophthalmological Society, December, 1907. I stated the contraindications. This was before the time when unfortunate experiences proved the correctness of my theoretical deductions. The prevention of reaction in the primary focus of the disease is the cardinal point.

Therefore, the conjunctival reaction is contraindicated if the eyes are or have been the seat of tuberculous disease, or even if there is a suspicion of the existence of such a lesion in the eye. Again application of the conjunctival reaction in an eye which has reacted is inadmissible and useless because it would bring about a reaction at what is practically a tuberculous focus. This would not have any diagnostic value. It would act just as a cutaneous reaction indicating a process which may have been latent. Another contraindication lies in the use of too concentrated preparations, especially the so-called "test" preparations. Their harmfulness especially appears when, as sometimes occurs, the conjunctival reaction is contraindicated for one of the reasons given above.

I recommend for use for the conjunctival reaction the "Ruete-Enoch† Tuberculin for Ophthalmo-reaction" in 1 to 2

†Made in Hamburg.

per cent. solution, the efficacy and safety of which I have tested; as to its activity I can vouch. With more concentrated solutions better statistics can be obtained, because in persons with active tuberculosis a higher per cent. of positive results will be produced. But I consider such statistics valueless, because they enforce a reaction in cases which are clinically evident, and in incipient cases my method gives such distinct signs that it is unnecessary to deviate from a harmless form of reaction.

In cases of tuberculosis in the early stages, the reaction used according to my directions give such distinct signs that no reason exists to vary my form of using the reaction, so often proved to be absolutely harmless. (A negative result of conjunctival reaction, in using the solutions I suggest, gives important prognostic evidence which is not to be obtained by the use of other concentrations.)

I admit freely that the ophthalmologists are competent to judge the value of the conjunctival reaction, but they must recognize the above mentioned contraindications and must get their experience from general medical cases. I am sorry to say that the ophthalmologists have hardly ever studied the contraindications, in consequence of which the conjunctival reaction will become prominent, only after overcoming many prejudices founded on ophthalmological publications.* It is not a mere coincidence that the ophthalmic clinic of Silex obtained very favorable results by using the method exactly according to my directions (tests made by Erlanger).

We have already said that the conjunctival reaction can be employed in diagnosis in internal medicine. But you will hear occasionally that the reaction is quite uncertain because it may be negative in tuberculous patients and positive in clinically healthy persons. This only confirms my statement and shows the clinical inexperience of the observer, because he does not appreciate that these negative reactions may be found in consumptives and that healthy people, who give positive conjunctival

**Wiener Klinischer Wochenschrift,* 1908, No. 33.

reactions should be regarded with ten times as much suspicion as those who react positively to a subcutaneous injection of tuberculin. And you know that many clinicians consider even such a subcutaneous reaction as quite important from a diagnostic standpoint.

Mistakes are also made concerning my opinion that there is a prognostic value to the reaction. Neverthless, I can state that this so seriously opposed opinion is coming slowly but surely to the front. Therefore, I am anxious to correct mistakes in literature. I declared that a negative conjunctival reaction is to be taken as evdence of unfavorable prognosis in manifestly tuberculous individuals (where bacilli are found), but I never said that a positive reaction indicates a favorable prognosis. Furthermore, I never stated that a negative conjunctival reaction occurring with a positive subcutaneous one indicated an unfavorable prognosis. In such cases I decide on a latent tuberculosis, while Ropke† actually states that I believe the opposite. This can be satisfactorily explained by the fact that Ropke and I differ in the interpretation of what constitutes an active tuberculosis.

The prognostic conclusions of Teichmann and myself * are based upon the course which the cutaneous reaction pursues. I wish it clearly understood that the prognostic deductions pointed out from the first by me have at least as great importance as the diagnostic ones, and have not been changed in any important features. This prognostic application is the reason why I practice both the cutaneous and the conjunctival reaction at the same time.

There is not, as may seem, anything mystical about making the prognosis depend upon the course of the reaction. Let us consider a continued reaction (Dauerreaction) which indicates, according to my conclusions, a cure or a favorable course. Such a reaction indicates that at the point of reaction the tuberculous

† *Brauer,* Klinik der Tuberkulose, Bd. 9, Heft 3.

**Berliner Klin. Wochenschrift,* 1908, No. 2.

poison causes a connective tissue formation. It is only necessary to suppose that the seat of disease reacts or has reacted in the same manner through the incorporation of these poisons, and then the result obtained by the continued reaction is easily understood. It is not to be wondered at if empirical observations have led to the same conclusions.

Here we find a strictly logical state of facts whose correlations are not at first recognizable. Wolfson and myself have made a great number of opsonic examinations, and we arrived at the conclusion that this trying procedure gives no better diagnostic results than an exact clinical examination in combination with the use of local reactions. The control of a tuberculin treatment by the determination of the opsonic index is another matter.

We supposed that we would find a high opsonic index in cases of strong tuberculin reactions, and particularly in cases showing a "Dauerreaction." This was not at all the case and it only gradually developed why this was so. A high opsonic index is produced by absorption of tuberculous poison from the focus of disease. This is prevented by the formation of connective tissue, which explains, therefore, the absence of a high opsonic index.

These opsonic experiments, together with our experiments concerning the binding of complements in tuberculous subjects,* prove that the poisons from the tubercle bacilli are absorbed, being identical in their effect with tuberculin. This fact is of great fundamental importance because it explains the difference in the opinions of many observers which could not otherwise be explained. It is well known that to-day there are adherents and opponents to the tuberculin treatment, from both a diagnostic and a therapeutic standpoint, the one side continuously reporting injurious effects which have not been observed by the other.

The above mentioned facts demonstrate that when a patient is injected with tuberculin, the same process takes place in him

**Wiener Klin. Wochenschrift,* 1908, No. 37.

which would develop eventually as the result of absorption of tuberculin from his own tuberculous lesions. Under these circumstances, it is dependent upon the point of view of the observer whether he holds the tuberculin injection or the disease itself accountable for the result. The same fact explains, it seems, what is apparently paradoxical, that the statistics of the adherents of tuberculin do not differ greatly from those of its opponents. I wish to state, *en passant,* that no good basis exists for the compilation of statistics of pulmonary disease. I shall discuss this on another occasion.

Inasmuch as in all tuberculous subjects tuberculin appears in the circulation, it can be easily understood that the results with or without tuberculin treatment can not differ very materially. It remains for the future to determine which individuals will require a tuberculin treatment. The observation of the local reaction, the study of the opsonins and the clinical course of the illness will be the determining factors.

Numerous experiments, the observation of local reactions and the work of others have convinced me, that there is a certain immunity in tuberculosis, an immunity against poisons which have become soluble and another against the bacilli themselves. The latter is most likely a bacteriolytic one. The immunity against poisonous matter, freed by lysis, is not an antitoxic one. but corresponds to the mechanism of the natural immunity against toxins which I have recently described.

The toxin immunity of the naturally non-susceptible animal consists of the binding of the poison by organ receptors (this stands in contrast to active immunity of an animal originally susceptible). If endotoxins are bound as described above for natural immunity, the fixation seems often to occur by means of the receptors in connective tissue.

Two cases will illustrate this: The cutaneous reaction was applied to both. They then received 1, 3, 5 mg. of tuberculin by subcutaneous injection and reacted with increasing fever. Using 7 and 9 mg., the general reaction did not occur, but in place of it an intense inflammation of the old cutaneous reaction appeared

(in one case erysipelas, and in the other an intense furuncle). These phenomena have been constantly produced by me in cattle. Their interpretation involves great difficulty and is only possible for those who have had an experimental training in the fundamental work of natural immunity against toxins. The tuberculin which has probably been made absorbable by lytic processes, is carried to those points where the receptors are located. These are essentially the foci of disease, but other places can act as foci with receptors. If all the tuberculin is bound here, a tuberculin injection will cause a local reaction. If it is only partially bound there will be a weakened or delayed local reaction and a late general reaction. We are thus enabled to protect the general organism from the influence of the tuberculin poisons by directing their action to less vital tissues, as, for instance, connective tissue, and we will probably be enabled to make therapeutic use of this fact. Taking it for granted that the protection of such receptors in the connective tissue will be of most advantage, and considering the numerous observations made by Hollender, Joseph, *et al,* that certain forms of skin tuberculosis preclude tuberculosis of the lungs, we can understand that after an injection of tuberculin the local reaction can appear before the general reaction, or even that the general reaction that is to be expected does not appear at all or is favorably influenced in its progress.*

For some time past I have been enabled by intracutaneous injections of small doses of tuberculin, or through the inunction of tuberculin ointment, to obtain in patients with lung disease artificial skin foci. In the second edition of my "Ophthalmodiagnose" it is my intention to give more accurate reports of the fundamental principles involved in this therapeutic measure, but I will not allow myself to be misled in reporting successful results too soon.

It can be easily seen how in this field purely theoretical with practical results are most intimately connected, of which

*Cf. Ophthalmodiagnose, Wolff-Eisner, Wuerzburg, 1908.

the conjunctival reaction, the initial step in our observations, is the most palpable proof.

I should like to call the attention of veterinarians to the fact that the application of the conjunctival method in cattle presented points of extreme difficulty. However, in the experiments that I have made with the aid of the agricultural department the principal difficulties have been overcome. It is to be hoped, therefore, that in the veterinary practice the conjunctival reaction will be developed in as exact a degree as in the human species.

In conclusion let me give a summary of my remarks:

1. The subcutaneous and the cutaneous methods are specific reactions for tuberculosis. As they both demonstrate latent tuberculosis, their use is extremely limited for clinical diagnosis.

2. The positive conjunctival reaction shows active tuberculosis.

3. The conjunctival reaction in clinically healthy individuals makes it particularly suspicious that they are affected.

4. A negative result in those manifestly tuberculous justifies a bad prognosis.

5. In advancing tuberculous disease negative reactions become more frequent.

6. A positive conjunctival reaction does not justify a good prognosis, but this is the case only in the so-called cutaneous "Dauerreaction," (continued reaction).

7. It is possible to create receptors in tissues that are indifferent as regards life such as connective tissue, these receptors attracting tuberculin and localizing the toxic action. This observation is of therapeutic value.

Closing Remarks.

Dr. Wolff-Eisner: Let me first thank Dr. Richard Wiener for translating my paper into English, and Dr. Libman for reading the same.

In my communication I could not give all the investigations concerning the theory of the action of tuberculin, especially the lytic theory of the tuberculin reaction. You can find the facts given in the first edition of my book, which was published in New York by Wood & Company about the 10th of October; new facts you will find in the *Berliner klinische Wochenschrift*, 1908. The second German edition of my book will soon be published. I hope you will enter upon the discussion of my paper without considering me a guest.

When I read my paper at the meeting of the German Medical Society last week, the chairman pointed out that the name "ophthalmoreaction" is a misnomer for several reasons. At the same time he stated my absolute priority. At the same meeting he said that I came to America to stand up for my rights. This was not my intention, because I thought there was no necessity, but yesterday while in the library of the Rockefeller Institute reading about one hundred papers of the American literature concerning the matter, I found only Calmette mentioned. I claim that I communicated the conjunctival reaction and discussion of the first paper of von Pirquet on the 15th of May, 1907, while Calmette made his communication to the Academy of Sciences in Paris, June 16th. To Calmette belongs the credit of having greatly assisted in having the reaction quickly adopted by the profession.

There can be no question about these facts: Calmette himself points out that the paper of von Pirquet was the cause of his investigations and this paper already contains my communicaton about the discovery of the conjunctival reaction. It is not generally known that on the same day on which Calmette read his paper, Vallee also read a paper concerning the conjunctival reaction in cattle, in which he stated that his investigations were undertaken in connection with my discovery.

Of greater importance to me than the question of the priority of the discovery of the reaction, is the part I took in building up the scientific structure which is based upon it, and its application for the prevention of tuberculosis. I should be

only too glad to work harmoniously with all those who have some aim.

There is no difficulty in applying the reaction, but the matter is not as simple as it may appear. It took my collaborators several months before they were able to carry out my intentions. In cases in which there is a contradictory result with the reaction, it is absolutely necessary to compare the results with the findings of the physical examinations if you want to avoid a wrong interpretation. If you can not exclude apparent contradictions, I would like to have you bring the matter before me. Many a physician has come to me with a very critical point of view, but no one has left me unconvinced.

Discussion.

Dr. Paul Courmont, Lyons, France: Dr. Wolff-Eisner's communication gives me the opportunity of saying a few words concerning the comparative value of the different diagnostic methods in testing for tuberculosis in which tuberculin is employed, and the so-called sero-diagnosis and sero-prognosis by means of agglutination. For the past ten years Dr. Arloing and myself have employed in Lyons, the sero-diagnostic method in cases of tuberculosis. This consists in making agglutination tests with the serum of tuberculous patients and the tubercle bacilli grown in homogenous cultures. This method has always given us excellent results, just as it has done in the hands of other investigators in Germany, Italy, and Sweden. It is easy to grow the tubercle bacillus in homogeneous cultures and to send such cultures from place to place for agglutination tests. We have sent from Lyons a number of cultures of our Bacillus "A" to different countries. The agglutination test is done in the same manner as in cases of typhoid fever. Only a few drops of serum are necessary for the test, and these may be obtained by pricking the tip of the finger or the lobe of the ear. If one compares this method with those in which tuberculin is employed (be it under the skin or in the eye) one sees that all these give similar results; but there are many advantages in favor of the sero-diagnostic

method. With all the methods the reaction is positive in a large number of cases of tuberculosis, and negative in very severe forms of the disease. With these three methods the reactions are positive in a sufficiently large number of subjects who are apparently in good health or in whom there are no clinical manifestations of tuberculosis. It is even more remarkable that the results obtained in non-tuberculous hospital patients are the same with the subcutaneous tuberculin method as with the agglutination test. About forty per cent. of such cases give positive results with the agglutination tests whereas forty-six per cent. are positive with the subcutaneous tuberculin test according to the statistics of 3,000 cases collected by Dr, Beck. This agreement of results shows that the two methods are equally good to indicate latent tuberculosis. In any event, if one should raise the objection to this method as being too sensitive and indicating the presence of tuberculosis where no other manifestations are present, then the same objection must be raised to the other methods used in the diagnosis of these cases. On the other hand the advantages of the agglutination test are the following:

First, The harmlessness of the method. The only operation which it is necessary to do upon the patient for this test is to obtain a few drops of blood from the tip of the finger—a procedure which is absolutely without danger. One can not say as much for the tuberculin tests. The injection of tuberculin under the skin can give general systemic reactions at times very annoying so that there is always required a certain amount of discretion in its use. The ophthalmo-reaction is subject to mishaps. In Lyons there have been observed a number of cases of severe keratitis. We have ourselves had one such case and several cases of severe conjunctivitis which lasted a number of days and gave rise to severe headaches. In a number of instances the patients have protested violently against the results of the reaction. The ophthalmo-reaction then has a number of objectionable features. One, perhaps, would say that these accidents are rarely found in a number of cases published, but it is sufficient that these accidents do happen; especially in view

of the fact that there are other methods of testing which are innocuous.

Second, Ease and rapidity of the test: A few drops of blood (one c. c. or thereabouts) are sufficient for the reaction. The test can be done in the laboratory away from the patient. After the blood is obtained the patient does not require any further observation on the part of the one performing the test. This, of course, is impossible with either the subcutaneous or ophthalmo-tuberculin tests.

Third, With the ophthalmo-reaction the patient can, in a way, tell whether or not the reaction is positive, which, of course, is a pernicious fact for those who may be affected by this knowledge. This, however, is not the case with the agglutination test.

Fourth, The possibility of making a local diagnostic test: We call this the local sero-diagnostic test, because the agglutination test may be made with the few drops of serum obtained from serous effusions, especially in cases of pleurisy. The reaction thus obtained gives proof of the localization of a tuberculous lesion. We have statistics of 120 cases of tuberculous pleurisy so examined. It is evident enough that such a local diagnostic test is impossible with tuberculin which gives only general proof of a tuberculous infection.

Fifth, Sero-prognosis by study of the variations in agglutination: The ophthalmo-test presents different degrees of reaction amongst different subjects, but these variations do not stand in close relations to the prognosis. The absence of an ophthalmo-reaction alone, in a tuberculous patient, seems to be a bad prognostic indication; the same is also true with the serum reactions. Furthermore, the variations in the agglutinating power of the serum of tuberculous patients are very interesting clinically. We have shown that agglutinating power rises when the patient makes good progress towards recovery and falls, on the other hand, when the case becomes more severe; agglutination at times disappears entirely in the period preceding death. One can draw very important con-

clusions in the study of the agglutinating power of tuberculous sera and their variations. We have shown by statistics of 112 cases of tuberculous pleurisy followed up for eight years that the pleuritics whose effusions (sero-fibrinous) agglutinated, recovered in 79 per cent. of the cases, whereas those whose effusions did not agglutinate, died in 73 per cent. of the cases.* It is therefore necessary to study the variations in agglutinating power of blood and serous effusions of tuberculous patients. Similar studies did not seem possible with the ophthalmo-reaction and it is also unwise to repeat the ophthalmo-tests in the same patient; and, furthermore, several inoculations of the conjunctiva with tuberculin seem to sensitize and give false results. It is therefore certain that all the advantages are in favor of the agglutination test.

In conclusion, I would insist upon making diagnostic reactions in the manner described. One is often wrong in asking whether agglutination and tuberculin reactions have absolute diagnostic value. There is no sign in medicine which is absolute or incontrovertible. The diagnosis and prognosis can be given only by assembling the different signs and not by selecting any one sign from all those present. The reactions of which I have spoken have by themselves only a relative value. They must be supported by clinical evidence in order that we may ascribe to them their full value. One should never rely upon these tests in the absence of all clinical evidence.*

Dr. Wolff-Eisner:. I agree with Dr. Courmont that one should use as many methods as possible; I have always asked that this be done. He is right when he says that the conjunctival reaction does not allow titration. If this is possible with the agglutination reaction it would be a great gain even if only for the reason that one could do without the inexact and time-robbing

*See P. Courmont: Sero-prognosis in Cases of Pleurisy, *Journal of the American Medical Association*, May 19, 1906.

*See P. Courmont: The Agglutinating Power in Tuberculous Patients. Sero-diagnosis and sero-prognosis: International Congress for Tuberculosis, Washington, 1908.

opsonic technic which I have been using to estimate the degree of immunity.

The opsonins really seem to go hand in hand with the agglutination, but the estimation of the agglutination was almost entirely dropped for this purpose. I would be very glad if Dr. Courmont would succeed in so developing the method that it would be a valuable addition to the conjunctival method. The findings of Dr. Courmont in typhoid and rheumatism, are absolutely opposed to my results. I have not found the conjunctival reaction present in the course of the study of very much material; for instance, in one hundred typhoid cases, I found the reaction only twice and in one of the two cases I later found tubercle bacilli.

A CASE OF TYPHOID FEVER ASSOCIATED WITH CHOLELITHIASIS, CHRONIC SUPPURATIVE CHOLECYSTITIS AND HEPATIC ABSCESSES,*

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Since the original publication in 1890 of Gilbert and Girode's article dealing with the occurrence of the typhoid bacillus in a case of suppurative cholecystitis, an abundant literature has accumulated, proving the frequent association of the typhoid bacillus with lesions of the biliary tract. As a result of the large number of casuistic contributions to this subject, it has been firmly established (1) that, during the course of a general typhoid in-

* Presented by Dr Martin at the October meeting of the New York Pathological Society, 1908.

fection, the typhoid bacillus regularly finds its way into the gall-bladder and is excreted with the bile; (2) that it may remain latent in the gall-bladder for an indefinite period of time without causing local lesions; (3) that typhoid bacilli persisting in the gall-bladder may be discharged into the intestine with the bile, and that such persons may, in this way, become "typhoid carriers" or distributors; (4) that the typhoid bacilli, instead of remaining as innocuous parasites in the gall-bladder, may form the nucleus for the development of calculi, or may cause a catarrhal or suppurative cholecystitis, with or without an infection of the biliary ducts; such an inflammation may occur in the course of a typhoid fever, or at any subsequent time; (5) that rarely, in the absence of any antecedent history of general typhoid infection, typhoid bacilli may cause "primary" lesions of the biliary tract. Such cases have been reported by Cushing[2], Wilson[3], Richardson[4], Guarnieri[5], Stewart[6], Burlew[7], Pratt[8], Bluementhal[9], Forster and Kayser[10], and others. Although the objection may always be advanced, that there may have been a previous mild attack of typhoid fever unnoticed or forgotten by the patient, the number of cases seems so great that it is pushing skepticism too far to deny the occasional primary localization of the typhoid bacilli in the gall-bladder.

The case here reported, though difficult of interpretation in some regards, is sufficiently interesting to merit consideration.

The patient, Jane S., was admitted to Bellevue Hospital on August 17, 1908, in the service of Drs. Le Fevre and Carlisle.

Family history negative.

Previous history. Had cholera morbus when a child, and "influenza" some years previous to present illness. One and a half years ago she was admitted to Bellevue Hospital.

The case on admission to the hospital was looked upon as one of acute lobar pneumonia, and acute gastro-duodenitis of alcoholic origin. After two or three days' observation and a closer investigation of the previous history, the jaundice and local abdominal signs, cholelithiasis was diagnosticated and the possibility of the correct diagnosis being typhoid fever then pre-

sented itself. The Widal reaction was returned as positive on the third day after admission, and a blood culture, taken on the second day following, confirmed the diagnosis by the presence of the typhoid bacilli in pure growth. The essential points in the history follow:

Jane S., aged 25 years, a housewife by occupation and the mother of two children, was admitted to Bellevue Hospital to the service of Dr. Egbert Le Fevre on August 17, 1908, at 1 p. m. with a temperature of 105° F., pulse 120, resp. 28. She had been sick nine days with dry cough, pain in the left side of the chest, vomiting and epigastric pain. She had been treated at a dispensary for dry pleurisy, had been drinking immoderately to dull the pain and distress. She had been jaundiced for five days and stools were alcoholic.

Past illnesses: Cholera morbus when a child, and influenza (?) some years ago. In February, 1907, was treated in Bellevue Hospital for gastro-enteritis. This attack was accompanied by severe pains in the epigastrium which radiated to the back, tenderness and vomiting. Though she has had similar attacks at various times since, she has never had jaundice before. These attacks were accompanied by dull aching pains in "stomach."

Present illness: Began in a manner similar to the previous attacks, but the symptoms of pleurisy soon developed. Had shortness of breath, dry cough and severe pain. Had no nose-bleed and no headache, no diarrhoea, no chill, no marked paroxysmal pain. Vomiting ceased two days before admission.

Physical examination: Medium sized, well developed, stout and somewhat anaemic, with marked icterus.

Lungs show consolidation of upper right lobe, with a few crepitant rales; dry pleurisy on left side at the base and slight general bronchitis.

Abdominal walls are thick with fat, soft, distended by tympanites. Tenderness in epigastric region and over gall-bladder area. No tumor.

Liver is easily palpated 3 inches below costal margin; edge smooth, tender.

Spleen, because of fullness in that region, is not palpable. Skin shows icteric hue; no roseola.

The patient's temperature ran a continuous course between 102° and 105° for three days, and then continuously between 102° and 104° for a week longer, dropping rapidly to normal on August 28, the twenty-first day of the disease; varied between 100° and 101° on the twenty-second day, when after a second drop to normal, it steadily rose, again reaching a point above 104° on the twenty-fifth day of the disease; became more remittent (101°-104°) till death on the twenty-ninth day (September 5). The pulse was rapid, feeble and dicrotic, ranging between 110 and 136 and later as high as 140-150. Respirations were rapid most of the time, 35-45-48. Lungs, upper left lobe, presented signs of consolidation on second day following admission. Distinct signs of resolution in both upper lobes were found on August 25. General bronchitis became more marked, numerous small and large rales and subcrepitant rales being heard over both lower lobes.

The patient complained frequently of severe pain in left lower axilliary region and on August 26, nine days after admission, of stabbing pains in right hypochondriac region. Examination of the gall-bladder area was always difficult on account of the abdominal distension, but a distinct rounded mass was felt apparently connected with the liver. Palpation of this tumor caused great pain. Ice bags gave some relief. Spleen was indistinctly palpable this day.

On August 29, the patient complained of considerable deafness, but no pain in either ear. On September 3, the left ear drum perforated and on the following day the right. A seropurulent discharge came from both ears.

The patient's general condition which was bad from the first, became very serious on August 31, and remained so until the end.

The blood examination showed a leucocytosis of between 13,000 and 35,000. The polymorphonuclear cells were relatively and absolutely increased (83-93%). The urine contained a

trace of albumin, bile and some hyalin and few granular casts. Diazo reaction positive.

Death took place on the twenty-ninth day of the typhoid fever. The jaundice remained, varying slightly in intensity on several days. There were no chills.

From the records of the necropsy performed by Dr. Pappenheimer, twenty-eight hours after death, the following notes may be abstracted:

Body is that of a quite well nourished female, apparent age thirty years. Skin and conjunctivae show a marked bright yellow icterus, and there is icteric staining of all body tissues and fluids. Panniculus is abundant. Musculature well developed but pale. On opening the peritoneal cavity there is found a small amount of somewhat sticky sero-fibrinous exudate in the dependent portions. A few fibrin threads are present on the visceral serosa.

Liver projects a hand's breadth below the ribs in the median line, and there are fresh fibrinous adhesions between the anterior surface and the diaphragm. The omentum is adherent both to the lower pole of the spleen and in the region of the pylorus and gall-bladder, where it forms a thickened, firmly adherent mass. The lower pole of the spleen reaches to the costal margin. The pleural cavities are free from fluid. Lungs are adherent to the diaphragm by a small amount of fresh fibrin.

Heart relatively normal in size. Right auricle is filled with yellow clot. Valves and orifices are normal. Musculature is strikingly moist, pale and flaccid. There are a few minute subendocardial petechiae. The aorta is delicate and free from atheroma throughout.

Lungs show fibrinous pleurisy, lobular pneumonia and bronchitis.

Liver weighs 2745 grams, and is enlarged in all dimensions. The surface, especially of the left lobe, is covered with a fine deposit of recent fibrin, and there a number of yellowish-green, raised prominences on the surfaces of all lobes, which on section correspond to collections of greenish pus. On section the left lobe of the liver is riddled with suppurative foci, which on

closer examination show a central yellowish core, surrounded by a greenish zone, corresponding in the gross everywhere to the small bile passages. The right lobe shows a smaller number of similar foci. On opening the duodenum, a thick, golden-yellow fluid, mixed with considerable detritus, exudes from the papilla, without exerting pressure on the gall-bladder. A probe passed into the duct from the duodenum enters the gall-bladder, and hepatic ducts without difficulty. The common duct, upon being split open, is found filled with thick, yellowish detritus, is everywhere widely patent, and contains no calculi.

Liver, stomach and duodenum were removed en masse, and an attempt made to dissect out gall-bladder and ducts.

The gall-bladder is buried in a mass of adhesions. The cavity is filled with the same thick, yellowish-brown material as the common duct, and shows a number of sacculated diverticula, containing smooth, non-facetted calculi, varying in size, the largest about the size of a cherry-pit. The precise relationship of the cystic and hepatic ducts to the gall-bladder cannot be made out; some of the calculi appear to be in the branches of the hepatic ducts. In all, there are about a dozen stones. On splitting up the intra-hepatic portion of the cava, there is found at the point of entrance of the left hepatic vein, a small thrombotic mass, about the size of a pea, and an underlying focus of suppuration in the vein and adjacent tissue. The portal vein is free from thrombus, and appears normal.

The spleen is slightly enlarged. The pharynx, larynx and trachea are normal. The stomach is normal. The small and large intestines are normal throughout, save that the mucous membranes are somewhat paler than normal. The Peyer's plaques and solitary follicles are not macroscopically visible, except by transmitted light. The intestinal contents consist of a small amount of unformed, bile-stained fecal material.

The lymph-nodes are very small, pale—without gross areas of necrosis.

The uterus, tubes and ovaries are practically normal. The kidneys show lesions of parenchymatous degeneration. The ad-

renals and bladder are normal. The brain is normal. Both middle ears are filled with greenish pus. The sphenoidal sinus also contains purulent exudate.

Anatomical Diagnosis:—Typhoid Fever; Suppurative Cholecystitis and Cholangitis; Cholelithiasis; Lobular Pneumonia; Fibrinous Pleurisy, Acute Bronchitis; Acute Sero-fibrinous Peritonitis; Suppurative Otitis Media, (Double).

Bacteriological Examination:—B. typhosus was twice isolated from the blood during life. Smears from the liver at autopsy showed numerous Gram-negative bacilli and a few Gram-positive, lancet-shaped, indefinitely encapsulated diplococci. Cultures were made from the peritoneum, liver, gall-stones, spleen and middle ear.

The gall-stones were carefully washed in 1:1000 bichloride and sterile water, and then washed in sterile Petri dish with broth, and plated on agar. Streak plates on ascitic agar were also made from the liver, in an attempt to isolate the diplococci. This was unsuccessful, plates being overgrown by the typhoid bacillus.

From the peritoneum, liver, spleen, gall-stones and ear, a motile Gram negative bacillus, giving all the cultural and fermentative reactions of the Bacillus typhosus was obtained, practically in pure culture. Positive agglutinations were also obtained with an immune rabbit serum of known titer.

Histological Findings:—Liver. Sections were taken for examination from various portions of the liver, and stained by the usual methods. The essential and most striking lesions found are widespread and irregular areas of necrosis, to which are added the evidences of an acute inflammatory reaction.

Taking for description such a necrotic area, we find a central bile-stained core, surrounded by a broad zone of disintegrating liver cells in every stage of necrosis. In many cases, such an area is sharply circumscribed and the adjacent liver lobules, though tangentially compressed, are well preserved. In other cases, the necrotic area is walled in by a broad zone of leucocytic infiltration. This is especially the case about the larger areas,

where it may be so extensive as to give them the character of abscesses. Bacteria (bacilli and cocci) may or may not be present in the necrotic areas; where found, they are situated principally in the central portions of the necrotic foci.

Striking changes are found also in the liver capillaries. Whereas the portal radicles and the hepatic arteries are distended with well-stained red blood cells, the capillaries themselves contain remarkably few well preserved red blood corpuscles. Instead, they are dilated and more or less filled with granular and hyalin detritus, and large cellular elements, which in many cases are attached to the capillary wall and may be definitely identified as swollen endothelial cells, or as dislodged parenchymal cells which have found their way into the capillaries as a result of the extensive destruction of the liver substance. Polynuclear leucocytes are found rarely; small round cells with intensely staining nuclei are more abundant.

In general, there is little increase in the interstitial tissue of the organ. In some regions, however, the periportal connective tissue is distinctly more abundant than normal, and evidence of recent proliferation is afforded by the presence of lymphoid and plasma cells and fibroblasts in considerable numbers. In the neighborhood of the necrotic areas, the periportal connective tissue frequently presents an edematous appearance.

The central veins are found in some sections filled with a structureless hyalin material, staining faintly blue with hematoxylin. The liver cells in the ventral portion of the lobules contain considerable bile-pigment, those of the peripheral portions often show a moderate grade of fatty infiltration.

The biliary ducts and the portal vessels, even those in close proximity to the necrotic areas, are absolutely normal. The significance of this unexpected finding we shall consider later.

The histological findings in the remaining organs may be passed over with a word. In the spleen, were found a few small areas of focal necrosis. In polychrome methylene blue preparations, a few short bacilli were found. Plasma cells were very abundant, many having two or three nuclei.

In the lungs, there is present an acute bronchitis and peribronchitis, with relatively large numbers of lymphoid and plasma cells in the exudate.

In summarizing the features of this case, we should like to emphasize the following points: The absence of any definite history of previous typhoid infection; the presence of vague symptoms of over a year's standing, referable to gall-stone disease; the sudden onset of an acute febrile disease, with icterus and other symptoms pointing to lesions of the gall-bladder and liver, and a complicating lobar pneumonia; the typhoid septicaemia. At the autopsy, we find a chronic cholecystitis with calculi, irregular necroses and abscesses in the liver, and as a result of the bacteriological examination, evidence of a generalized and local infection with the typhoid bacillus. On analyzing this case, especially as regards the sequence of the various lesions, we meet with various problems. The important question as to whether the typhoid cholecystitis was a primary infection, or the sequel of an unrecognized typhoid infection at some previous time, it is impossible definitely to decide. Possibly the illness described as influenza may in reality have been a mild typhoid. Details are wanting, but that the typhoid cholecystitis was of long standing, is evident from the character of the lesions. The lesions in the liver are especially difficult to interpret. The study of the sections seems to indicate that the essential histological feature is a necrosis of the liver cells, and that the inflammatory changes observed about some of these areas are of secondary importance. The marked lesions found in the capillary endothelium would perhaps suggest a primary toxic influence as a principal factor in the causation of the lesions. Although occasional organized parietal thrombi were found in some of the branches of the portal veins, and more recent hyalin thrombi in some of the hepatic veins, it seems hardly warranted to ascribe the wide-spread liver necrosis to these factors, particularly as there is no affection of the larger portal vessels. The biliary ducts, with few exceptions, are normal, so that there is no ground for considering the liver lesions as caused merely by an infectious cholangitis. We can

only say that in the course of a chronic typhoid infection of the gall-bladder, there developed an acute typhoid septicemia, associated with marked necrotic lesions in the liver.

Of course, it is not possible to say that the patient was a typhoid distributor, but in view of the recent German research work, and the case so well described by Soper, it certainly appears probable.

We desire to express our thanks to Dr. Alwin M. Pappenheimer for his assistance, encouragement and advice.

REFERENCES.

1. Gilbert et Girode: Contribution a l'étude bacteriologique des voies biliares. Comptes rendues de la Soc. de Biol. 1890.

2. Harvey Cushing: Typhoidal Cholecystitis and Cholangitis. *Bull. Johns Hopkins Hosp.* 1898, p. 91.

3. O. S. Wilson: Primary Typhoid Cholecystitis and Cholangitis. *Jour. Am. Med. Assn.*, 1908, May 16, p. 1607.

4. Richardson: Cholecystitis due to Typhoid Bacilli, *Boston Med. & Surg. Journ.*, 1897, Dec. 2, p. 570.

5. Guarnieri: Contributazione alla patogenizi delle Infezione Biliari. *Rev. Gen. Ital. di Clin. Med.*, 1897.

6. Stewart: Primary Typhoidal Cystitis with Calculi. *Am. Medicine*, 1904, vol. vii, p. 1018

7. Burlew, J. M.: Typhoid Cholecystitis with Calculi, without Evidence of Typhoid Fever. *Medicine*, Oct. 1903. (Abstracted in *Am. Med.*, 1903, vol. vi, p. 959.)

8. Pratt: Typhoid Cholecystitis with Observations upon Gallstone Formation. *Am. Journ. of Med. Sciences*, 1901, vol. 122, p. 584.

9. Blumenthal, T.: *Münch. Med. Woch.*, 1904, No. 37.

10. Forster & Kayser: Ueber das Vorkommen von Typhusbazillen in der Galle von Typhuskranken und Typhusbazillenträgern. *Münch. Med. Woch.*, 1905, Aug., p. 1473.

11. Soper: Work of a Typhoid Distributor. *Jour. Am. Med. Assn.*, June 15, 1907.

ADENOMYOMA OF THE ROUND LIGAMENT.

F. C. WOOD, M.D.

Dr. F. C. Wood presented a specimen which had been removed from the inguinal region of a patient at the German Hospital during the course of an operation for inguinal hernia. The history of the woman was of no especial interest. In the resection of the hernial sac this nodule was removed. It was a small, oval mass, about 2.5 x 1 cm., occupying part of the wall of the sac. This was cut, and in the sections there was found, besides muscle fibers and fibrous tissue of the round ligament, a number of alveoli lined by high cylindrical epithelium. There were no cilia on these epithelial cells. The alveoli were surrounded by tissue suggesting the structure of the endometrium. The morphology of these alveoli in the round ligament tumor was similar to that of the alveoli of adenomyomata of the uterus. The specimen was shown merely because it was somewhat of a pathological rarity, only about eight cases having been described.

SPECIMENS FROM A CASE OF GASTRO-INTESTINAL PSEUDOLEUKEMIA.

H. L. CELLER, M. D.

The specimens demonstrated were obtained from a man, forty-eight years of age, admitted to the surgical service of Mt. Sinai Hospital in September, 1907. The clinical history may be briefly given. For about a year the patient had noticed a large, irreducible mass in the left inguinal region. The day before admission he was attacked with abdominal cramps and repeated vomiting. The bowels were moved with enemata. There was slight fever. One year previously the patient had had a similar attack that subsided spontaneously.

The patient was admitted to the hospital with the diagnosis

of acute ileus. It was noted in the physical examination that he was quite anemic and emaciated. The mass in the left inguinal region was described as being about the size of a fist, hard, not tender, not reducible. The blood count showed 10,600 white cells, seventy per cent. of which were polymorphonuclear leucocytes, thirty per cent. lymphocytes. No abnormal cells were present. Urinary findings negative.

At operation, the inguinal mass was found to consist of a packet of lymph nodes of varying size. The individual nodes could be readily distinguished in the tumor. Abdominal section revealed an intussusception at the ileo-cecal valve, and, as reduction could not be effected, the intussusceptcd portion of intestine was resected. The patient's condition, which was very poor before operation, rapidly became worse, and death ensued shortly after his return to the ward.

The autopsy was performed a few hours later by Dr. E. Libman, whose report is here abstracted.

The right cervical lymph nodes are slightly enlarged. The thoracic viscera show only minor changes. There is no enlargement of the mediastinal or bronchial nodes. The liver is slightly enlarged, firm, and shows congested central veins. In every cut section there are visible one or more firm, yellow tumors, varying in size from a pinhead to one centimeter in diameter. The spleen is very slightly enlarged; lymphoid follicles prominent. With the exception of the stomach and intestines the remaining abdominal organs are negative.

Stomach:—Thickly studding the mucous membrane of this viscus are circular or oval elevations which vary from one millimeter to one centimeter in diameter, yellowish-white or pink in color, almost diffluent in consistency. The larger masses project into the cavity of the organ as sessile polypi. The smaller ones form flattened, frequently coalescing infiltrations immediately beneath the mucosa which is apparently thinned out over them. Toward the pylorus the walls are considerably thickened. These changes are most marked on the anterior and

posterior walls of the stomach; the pyloric antrum is entirely free from evident lymphoid tissue.

Duodenum:—The upper six centimeters show marked hyperplasia of the lymphoid tissue in the form of large polypoid masses elevated one-half centimeter above the mucous surface, and presenting free, overhanging edges. In color and consistency theses masses are identical with those already described in the stomach. The lesion ends abruptly, leaving the remainder of the somewhat dilated and congested duodenum free.

Intestines:—Here the lymphoid filtrations invade for the most part the Peyer's patches, which vary very considerably in size, measuring from one and one-half to eight centimeters in length. All are pigmented, black or brown in color, of irregular outline, the larger plaques showing various stages of superficial ulceration or necrosis. They resemble the agminated patches found in the stomach in that they are composed of a number of smaller, coalescing nodules; they differ, however, in that the overlying mucosa is elevated from one-half to five millimeters above the surface of the intestine. These plateau-like tumefactions bear a close resemblance to certain types of carcinoma. The most marked changes are found in the neighborhood of the ileo-cecal valve, where fungoid masses larger than those in the duodenum are present. This is also the site of the most extensive ulceration, some of the lesions resembling those found in the early stages of typhoid. In both the large and small intestine, notably in the ascending colon, the solitary follicles also present evidences of involvement. The larger follicles are about the size of a split-pea, and resemble ordinary warts, but are softer in consistency. Some of them are hemorrhagic.

Surrounding the pancreas near its upper border, there are many enlarged, elongated, lobulated lymph nodes, soft in consistency, pink or yellow in color. The lymph nodes along the greater curvature of the stomach present similar changes.

Miscroscopically the gastro-intestinal infiltrations are seen to be composed almost wholly of densely packed lymphoid cells of the type usually present in these situations. These cells are

mostly confined to the submucosa, although in the larger lesions they are sometimes seen to invade the mucosa, lying between the glands. The muscular coats are nowhere infiltrated.

A similar picture is presented by the lymph nodes, where the cellular increase is so great that neither germinal centers nor sinuses can be differentiated. Irregularly scattered among the lymphoid cells are giant endothelial cells containing from one to four pale-staining, irregular nuclei. A few polynuclear eosinophiles and red blood cells are also present. Each node is sharply outlined by a slightly thickened capsule from which, in one of the largest nodes, a few narrow strands of dense fibrous tissue penetrate among the lymph cells for a short distance. There is no infiltration of the capsule, although small collections of lymphoid cells surround some of its vessels.

The enlarged Malpighian corpuscles of the spleen, as well as the yellowish areas in the liver, also contain cells of the type found in the intestinal infiltrations. In the liver the cellular masses are confined wholly to the region of the portal vessels.

Seven typical cases of lymphoid hyperplasia confined to the gastrointestinal tract are collected in a paper published by Wells (1), under the title, "Pseudoleukemia Gastro-intestinalis." To these Wells has himself added one case, while still another has been since published by Hoffman (2). Even a cursory study of the literature demonstrates that a considerable variety of conditions has been heretofore described under this head. The work of Reed, Longcope and others has established Hodgkin's disease as a distinct pathological entity. Excluding this group, the confusion that has arisen concerning the cases under discussion might be best removed by adopting the ingenious and comprehensive classification suggested by Türck. In view of the absence of blood changes as well as of evidences of malignancy, this series of cases would then fall in the category of "alymphemic lymphomatoses."

(1) *American Journal of the Medical Sciences,* November, 1904.

(2) *Archiv für Klinsche Chirurgie,* 1907.

Discussion.

Dr. W. T. Longcope said that he had been very much interested in examining the specimens in this case. This type of simple hyperplasia or increase of the lymphoid cells, which Dr. Celler had described, must certainly be an unusual condition. He would like to ask whether there were any bacteriological examinations made in this case. The case was certainly not a lymphosarcoma.

Dr. James Ewing said that he had no more definite ideas in regard to the nature of the disease than Dr. Celler had expressed. It seemed to him that it was a very important case and suggested to him transitional stages between cases which he had seen, and between which he had wondered if any relation existed. These were the so-called typical small cell lymphosarcoma, certain cases of Hodgkin's disease, and status lymphaticus. In all of these conditions it seemed to him that one had to deal with a systemic disease of the lymphatic apparatus. Lymphatic leukemia was another disease of the same class. The description of the lesions in this case was almost identical with that of some cases of status lymphaticus, although he had never before seen such widespread hyperplasia in the latter condition. Dr. Ewing had published a case some years ago, in which the lymphoid tissues were extensively hyperplastic, much more so in the Peyer's patches than in this instance, but in which there was no involvement of the nodes about the pylorus. The present case seemed to him suggestive as possibly standing between status lymphaticus and general lymphosarcomatosis.

Dr. Celler said that no bacteriological work had been done on the case. Neither blood cultures nor animal inoculations were made. Microscopic examination of the lymph nodes might at first suggest the possibility of the case being one of Hodgkin's disease on account of the slight increase in connective tissue, and the presence of multinuclear giant cells. Here, however, all resemblance between the two conditions ceased, and, as Dr. Ewing himself had said, the case was evidently not one of Hodgkin's disease. Marked hyperplasia of the Peyer's patches

is not uncommon in status lymphaticus, although both the gross and microscopic appearances differ from those presented by the demonstrated specimens. Against the diagnosis of lymphosarcoma may be cited the uniformity presented by the lymphoid cells, which correspond exactly with those normally present in the lymph nodes and intestinal tract; and the absence of karyokinesis, of metastases, and of infiltration of the muscular coat of the intestine as well as of the capsules of the lymph nodes.

A STUDY OF CASES OF HODGKIN'S DISEASE AND LYMPHOSARCOMA.

W. T. LONGCOPE, M. D.

In presenting this subject, Dr. Longcope said that he felt some embarrassment by reason of the fact that he had so little new to show; but it had occurred to him that it might be of interest to give the results of a study of a certain number of cases of progressive enlargement of the lymph glands observed at the Pennsylvania Hospital, and to compare the pathological changes in the lymph nodes from these cases with the alterations in a series of lymph gland tumors which were now being investigated. The material for these latter observations had been kindly sent to him from a number of different laboratories.

Altogether at the Pennsylvania Hospital, twenty-five cases had been studied, in which the disease was characterized by a progressive enlargement of the lymphatic glands, either generalized or of a single group. These twenty-five cases had been followed, unfortunately, most of them to the autopsy table. Out of the twenty-five, the lymph nodes from twenty-one presented characteristic pathological changes, both in the gross structure and in the histological structure. These changes, which were later shown more readily by means of lantern slides, were much the same as those recognized for a number of years, but to which

Reed first called attention in this country, and considered characteristic of Hodgkin's disease. The pathological picture in all of these twenty-one cases had corresponded quite accurately, though there had been minor differences.

Four cases were of an entirely different nature. These cases were characterized by a growth in the lymph glands of a cell of one type. In three cases this was a large cell, much larger than the small lymphocyte, and almost as large as the cell which forms the mass of the germinal centers of the lymph follicles. The cell sometimes infiltrated the gland, though it did not replace the actual lymphoid structure. One case had died; two were still living and under observation. The fourth case represented still another type of growth. In this case the cells were small and somewhat irregular, and entirely replaced the lymphoid structure, forming, by an infiltration of the surrounding fat lobules, tumors which looked in themselves much like lymph nodes. The cells forming the growth showed numerous karyokinetic figures. This patient died within a year.

Dr. Longcope said that in this study he had excluded all cases of definite tuberculosis, as well as cases of syphilitic enlargements of the lymph glands, and cases of certain rare tumors of the lymph glands.

In regard to the diagnosis during life between some of these conditions, Dr. Longcope said that as every one had recognized, it was often a very difficult matter to differentiate between Hodgkin's disease and tuberculosis, Hodgkin's disease and lymphatic leukemia occasionally, and Hodgkin's disease and sarcoma —those cases in which there was a growth of one particular type of cell in the lymph glands. From tuberculosis, in the very vast majority of cases, the differentiation was not a very difficult matter; but certain cases of acute tuberculosis of the lymph glands it had been found very hard to differentiate from Hodgkin's disease. This type of tuberculosis, in which minute tubercles are scattered throughout the gland tissue, may be present for some months; the glands may not be very large and may be quite movable; but they usually at some time give pain, an im-

portant point in the differentiation of the condition from Hodgkin's disease. Without a histological examination of the gland itself or without a tuberculin reaction it may be impossible to differentiate the two conditions. From another type of glandular tuberculosis it was also difficult to separate these cases; that is cases in which there was an extensive caseation of a large number of lymph glands in various situations in the body. These cases may be differentiated by a tuberculin reaction.

From lymphatic leukemia it is always possible to differentiate cases of Hodgkin's disease by means of the blood count. Only during the remissions in lymphatic leukemia may the two diseases be confused. In the cases of Hodgkin's disease examined, there has usually been a polymorphonuclear leucocytosis; occasionally the leucocytes were low, 6,000 to 10,000; usually they were about 30,000. In two cases there was a moderately marked eosinophilia. Much stress could not be laid upon this fact, however, though it was interesting in connection with the presence of great numbers of eosinophiles in the lymph node tumors in some cases.

From lymphosarcoma it had been almost impossible to differentiate Hodgkin's disease from clinical examinations alone. None of the cases were diagnosed before the glands were removed.

To compare with these twenty-five cases, Dr. Longcope was now studying tissue from another series. So far examinations had been made of tissue from forty-seven cases. Of these, nineteen corresponded exactly with the findings in the twenty-one cases of Hodgkin's disease; seventeen apparently belonged to the sarcoma group, showing the growth of one particular variety of cell; two were definitely mixed celled sarcoma; and two were cases of lymphatic leukemia. The histories had shown that these last two cases, although they had remained for months with a low leucocyte count with only 20 to 30 per cent. of lymphocytes, had at times had as many as 30,000 to 60,000 leucocytes with 90 per cent. lymphocytes.

Finally, in reviewing the literature, seventy-four cases had

been collected, principally from German sources, in which the descriptions were quite accurate, and corresponded exactly with the type of curious granuloma-like tissue which had been found to be characteristic of the cases of Hodgkin's disease studied.

Dr. Longcope further said that the main problem at issue was the etiology of these conditions. He had inoculated animals—guinea-pigs and rabbits—with material from twelve cases of Hodgkin's disease, without finding tuberculosis in any of them. Monkeys had also been inoculated with lymph nodes from two cases, and the results were rather interesting, but not conclusive. After subcutaneous inoculation there was general glandular enlargement, which made its appearance in about three weeks; no changes occurring before that time. The glands became so large that they could be readily seen in the cervical region and in the axilla. Some of these glands were removed and showed histologically only simple hyperplasia. There were none of the characteristic lesions of Hodgkin's disease. After about two months the glandular enlargement subsided entirely. He had tried again to produce glandular enlargement with the same tissues, but after keeping the tissues on ice for several weeks they produced no effect when inoculated into monkeys. The fact that glandular enlargement could be obtained might depend simply upon the injection of large amounts of foreign cellular material.

Fresh tissue had been stained in many ways, and nothing characteristic of any organism had been found. Sections were stained by the Levaditi method but no structure which could be identified as spiral organisms could be found. No clue could be given, therefore, as to the etiology of the disease. However, it seemed at present that it would be much better to limit the term Hodgkin's disease to the type of tumor described, which is sufficiently characteristic to enable one to differentiate it from other type of growths in the lymph glands. Until something definite was known as to the etiology it was, of course, impossible to make any rational classification. Until then it seemed best to differentiate these cases of Hodgkin's disease from various types of sarcoma of the lymph nodes.

Discussion.

Dr. F. C. Wood said that he had recently seen a case in Dr. John S. Thacher's service at the Roosevelt Hospital which was of interest in this connecton. The autopsy was performed by Dr. Hodenpyl. The patient was a young boy on whom a diagnosis of anemia had been made. The only lesion found was enlargement of the spleen, which contained large yellowish masses and a few hard lymph nodes. None of these nodes were very large but they were very hard. The bone marrow was not involved. The microscopic sections of the spleen showed large Malpighian follicles with lymphocytic type of cells. The yellowish areas were dense connective tissue with some necrosis and some hyalin degeneration. The nodes were almost entirely fibrous tissue. In a few small areas in each node there were areas of lymphoid tissue with a few large cells with lobulated nuclei as in the ordinary Hodgkin's disease. There was no lesion in the intestine and except for the general anemia the lesions in the spleen and lymph nodes were the only ones found.

Dr. James Ewing said that he would prefer not to attempt to discuss the subject without notes, and would rather simply express his gratification at having listened to the presentation. He might perhaps tell of his own experience with cases clinically called Hodgkin's disease. They were very common in New York. As Dr. Longcope had said, we are very much in doubt as to what cases to group together. Dr. Ewing's own rule was when such nodes were sent to the laboratory for examination to class as Hodgkin's any case with a clinical diagnosis of Hodgkin's unless it showed a perfectly definite lesion of some other type, as sarcoma. Of the group classed as Hodgkin's the majority were found to be of the giant cell type, though a large proportion were of the small cell type without giant cells, pure lymphocytes, with obliteration of the lymph follicles. Some showed very marked development of giant cells; others showed marked development of hypertrophied endothelial cells. He had recently seen such a case from the New York Hospital, in

which almost the whole tissue was made up of endothelial cells. In other cases the numbers of eosinophiles were astonishing. There were in this group of cases a number of other very peculiar histological structures, the significance of which he was quite unable to determine. In regard to the etiology, Dr. Ewing said that his own belief had been very much colored by a publication by Sternberg, in which was described a peculiar type of tuberculosis of the lymph nodes, exhibiting the histology of giant-cell Hodgkin's disease. The clinical history was similar to Hodgkin's disease, and tuberculous infection had been demonstrated. He did not share the belief of those who held that tuberculosis had been eliminated as an etiological factor in Hodgkin's disease. He had looked over many slides in the search for tubercle bacilli, but the results were almost invariably negative. In studying one case which had been sent to him, Dr. Ewing had spent an entire afternoon searching the sections, and had finally succeeded in getting a few acid fast bacilli in the nodules in the liver. His own feeling was that eventually it would be found that this disease falls into the group of peculiar lesions of tuberculosis. He had inoculated animals with the nodes repeatedly, and the results had not been entirely negative. Dr. Ewing thought Dr. Longcope's contribution most admirable, and hoped that he would continue his experimental study and throw still further light on the etiology.

Dr. Richard M. Pearce said that as most of his knowledge of Hodgkin's disease had been obtained from Dr. Longcope while he was associated with the latter in pathological work in Philadelphia, he had nothing of value to add to the discussion. In regard to Dr. Ewing's remarks as to the possibility of a tuberculous nature of the lesions, Dr. Pearce said that he had thought that this opinion had been rather generally set aside. He believed the differentiation which Dr. Longcope had attempted, even though it were not final, was of great value, because it gave two or three groups into which doubtful cases could be thrown until etiological or other investigations offered a sound classification of these puzzling affections of the lymph nodes.

Dr. E. Libman referred to a few cases of some interest which he had seen. One was a case of Hodgkin's disease with a high leucocyte count, 35,000 to 40,000, with high polynuclear percentage. The patient was intensely jaundiced. At autopsy destructive and secondary fibrous changes in the tissue were very marked, apparently due to long-continued X-ray treatment. The X-rays had been applied to the axilla and the enlarged glands had disappeared. The high polynuclear count was interesting, as there was no diffuse polynuclear infiltration in the tissues. Cases in which the lesions were confined to the abdomen were also of interest. In one interesting case which he had seen the patient had pain in the abdomen and was jaundiced, and was operated on for supposed gall-bladder disease. Large lymph nodes were seen, and the post-mortem showed Hodgkin's disease, although the lesions themselves showed no tubercle bacilli. The patient was a man who had had continued fever, and hemorrhages from the nose and throat. The patient stated that he had had lymph nodes removed from the right axilla two years before. The lymph nodes in the left axilla were enlarged and there was some bleeding from the nose and throat. The white cell count was about 5,000; the red cells were increased in number and the hemoglobin was over 100 per cent. The question arose as to how to account for the polycythemia, and the most likely thing seemed tuberculosis. It was thought that the symptoms were due to a miliary tuberculosis, and before the patient died miliary tubercles were found in the choroid. The post-mortem showed general miliary tuberculosis which was very extensive. There was a new formation of red blood cells in the bone marrow; and a most interesting thing was that the lymph nodes at the root of the mesentery contained old cheesy foci. In some of them the cheesy areas were surrounded by tissue quite typical of Hodgkin's disease. His own experience had been similar to that of others in that he had not been able to prove tuberculosis to be the etiological factor. He believed in grouping together all of these cases as Dr. Longcope had suggested. The problem was the same as in certain cases of icterus

and the erythema group. It was probable that although a number of cases in the group were due to one cause, other causes could produce similar lesions.

Dr. Longcope said that Dr. Ewing had spoken of caseation in some glands. They had seen this condition several times, and in two cases had inoculated guinea-pigs with masses of material and portions of the glands, but had not found tuberculosis. There was a type of necrosis which sometimes occurred in these cases, but so far he had not been able to show that this was due to the tubercle bacillus. Dr. Libman had mentioned the effect of the X-rays upon these glands. This he had noticed in one case. It was quite remarkable to see the change which took place in the glands. The lymphatic tissue apparently disappeared. A gland removed after X-ray treatment showed a curious fibrous condition with a few masses of cellular material scattered here and there. The lesions which had been strictly confined to the abdomen they had not seen very frequently. In only one case were the spleen and mesenteric lymph nodes found enlarged; this patient had come to autopsy. In another case there was involvement of the inguinal glands and of the retroperitoneal.

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DR. E. LIBMAN, *President.*

AN EXPERIMENTAL STUDY OF THE METABOLISM AND PATHOLOGY OF DELAYED CHLOROFORM POISONING.

JOHN HOWLAND, M.D., NEW YORK, AND A. N. RICHARDS, PH.D., CHICAGO.

(From the Laboratories of Pharmacology and Pathology of the College of Physicians and Surgeons, Columbia University, New York.)

In the course of some investigations which have occupied the attention of Dr. A. N. Richards and myself during the past four years, we used prolonged and repeated inhalations of chloroform in an attempt to diminish the oxidative power of the cells and thus to inhibit or prevent the transformation of certain

substances with which we were experimenting. We found, however, that a number of control animals which received chloroform alone were profoundly affected and died after a lapse of hours or days after their return to consciousness and that they all exhibited severe parenchymatous lesions, especially in the liver. In other words, we produced typical delayed chloroform poisoning. It appeared to us advisable, in view of the great importance attaching to delayed poisoning, to study the metabolic changes occurring as a result of this, and in comparison with the pathological lesions produced. Dogs, upon which metabolic experiments are most easily carried out, can also be regularly so anesthetized as to cause their death many hours after the anesthesia.

The conception of delayed chloroform poisoning has been of slow development. Although Casper[1] and Langenbeck[2] in 1850, and Mouat[3] in 1856 spoke of a postponed fatal effect of chloroform, it was not until more than thirty years later that the condition began to be generally recognized and accepted. Thiem and Fischer[4] in 1890 also reported a fatal case due, they believed, to the delayed effect of chloroform. In the following year Bastianelli[5] reported three cases, and in 1892 Fränkel[6] reported several more. Thereafter reports appeared in rapid succession by Ambrosius[7], Guthrie[8], Bandler[9], Marthen[10] Heintz[11], Steinthal[12], etc. In England Guthrie's paper first called attention to the condition, and in this country cases have been reported by Brewer[13], Bevan and Favill[14], Holmes[15], Cushing[16], Ballin[17], Wells[18] and others. It is undoubtedly true that some deaths have been reported as due to chloroform which could, with greater probability, be referred to some other cause, such as the original disease or the strong antiseptics employed; but this does not affect the validity of the majority of reported cases.

It is held, and the published accounts bear this out, that the liver changes in fatal human cases vary according to the age of the patient; that those in the very young differ from those in older children or adults in the *absence of necrosis*. It is dif-

ficult to understand such a selective action. Two explanations are possible: The first is that in young children the duration of symptoms is usually less than twenty-four hours; and it may be that death occurs before the lesions have had full time to develop. The second is that the majority of instances of this type were reported before the necrotic nature of the lesions was well recognized (1896) and the published autopsy findings were very incomplete and unsatisfactory.

It seems likely that in some instances at least the true character of the lesions was not recognized. Guthrie[19], in his second paper, reported the case of a child, three years old, who died eighty-four hours after operation. Fatty changes in the liver are alone described, but a photomicrograph is given of a section stained for fat, in which the whole center of the lobule seems necrotic. Nevertheless it must be admitted that there are on record fatal cases of delayed chloroform poisoning which showed at autopsy, so far as reported, only fatty changes in the liver. In the older or so-called cholemic type the lesions in the parenchymatous organs, especially the liver, are severe and vary in the different cases only in degree. There is almost always an intense icteric discoloration of the skin. There may be cutaneous hemorrhages; and hemorrhagic extravasations into the serous membranes of the abdominal and thoracic cavities are frequently found. There may also be areas of hemorrhage in the gastrointestinal tract. The heart is seldom macroscopically altered. With appropriate staining, fat in greater or less quantity may be demonstrated in the fibers. The kidneys always suffer to a certain extent, though the evidence is frequently only microscopical. Whatever fatty change is present is apt to be in the collecting tubules. The cells of the convoluted tubules show all degrees of degeneration, and scattered cells may be necrotic. The glomeruli escape.

The volume of the liver varies with the duration of symptoms. The longer death has been postponed, the smaller is its size. The color is usually strikingly yellow, "saffron" or "ochre colored" it is often called, and at times it is mottled with pink-

ish areas. On cross section the lobular markings may be difficult to distinguish, or it may be noticed that the lobules are yellowish or grayish at the periphery and reddish in the center.

Under the microscope all grades of destruction are found, from the slightest necrosis in the center of the lobule to almost complete dissolution of the whole parenchymatous structure of the organ. The essential lesion is necrosis; it begins at the center of the lobule and advances centrifugally. In some instances, those that have been described as acute yellow atrophy, the liver structure has been almost unrecognizable. At the periphery of the lobule in contact with the portal spaces are cells retaining their normal form and staining properties, but all the cells not necrotic are heavily loaded with fat. The protoplasm of the necrotic cells may be retained and stain deep pink with eosin, or it may have been almost entirely removed and only a narrow rim be left around the fragmented nucleus. The center of the lobules may show great congestion and even hemorrhage. In striking contrast to this destruction of parenchymatous cells is the normal condition of the bile ducts, blood vessels, and connective tissue.

Nothnagel[20], in 1886, was the first to study the lesions produced by chloroform in animals. His experiments were badly planned in that he gave chloroform by mouth and subcutaneously, and not by inhalation. The amount that he employed was, moreover, so very large that most of the animals died in a few hours, or were killed at that time. Nevertheless he produced fatty changes in the heart, liver, and kidneys.

The first attempt to explain delayed poisoning was made in 1883 by Ungar with the help of Junkers[21]. He appreciated the great difficulties in the way of separating symptoms and pathological changes due to chloroform, from those due to the primary disease or injury necessitating operation, and therefore decided to use animals. His experiments were carefully planned and carried out, and his results were of great importance. He administered chloroform by inhalation to rabbits and dogs, and was able to produce great fatty changes in the

liver and heart and less in the kidneys. Unlike most subsequent investigators, he let his animals die, and so obtained more severe lesions than have those who after twenty-four, forty-eight, or more hours, killed their animals. Like many who followed him, it is evident that he began with a preconceived idea as to the organ most probably responsible for death, and wrote his descriptions of lesions from that standpoint. He found great change in the cardiac muscle and inclined to this as the cause of death. From his description of the appearance of the livers, both macropscopical and microscopical, it is apparent, however, that in them very severe lesions were present. He says that the center of the lobules was made up of only fatty detritus, the cell outline was indistinguishable.

In 1889 Ostertag[22] and Strassmann[23] independently confirmed Ungar's findings.

Thiem and Fischer[24] in 1890 used rabbits and dogs and produced marked fatty changes, especially in the livers. In 1896 Bandler[25] and Heintz[26], independently, recognized necrosis in the livers of fatal human cases and produced necrotic lesions in the livers of dogs and rabbits. From this dates the recognition of necrosis as the most important of the changes produced by chloroform. In fact hardly an autopsy has been reported since that time that has not shown necrosis, and in many it has been so marked that the cases have been denominated acute yellow atrophy.

There has been practically complete agreement among all writers during the last ten years that the most extensive changes are produced in the liver, and that here is to be found the chief cause of death. Offergeld[27] alone dissents from this view and thinks the kidneys the organs chiefly involved.

There is no record in the literature, so far as we know, of a study of the metabolism in animals in which such a condition of delayed chloroform poisoning has been experimentally induced. The metabolic effects of chloroform given by mouth, by subcutaneous injection, or by inhalation, have been widely studied, but in every case normal, uneventful recovery apparently

occurred. Strassmann[28] made estimations of the urinary nitrogen before and after chloroform inhalation. There was a marked increase in the nitrogen excreted. Salkowski and Taniguti confirmed this. Kast and Mester[29] examined changes in the sulphur excretion after anesthesia with chloroform in human subjects. They found marked changes in the ratio of sulphate sulphur to neutral sulphur, the latter form being increased greatly in amount, the former being little affected.

In 1897 Vidal[30] published the results of a very comprehensive study of the effect of chloroform on metabolism. Some of the methods which he used are now open to serious criticism. Urea, for example, was estimated by the hypobromite method, and creatinin by the old Neubauer method. The results of a number of observations on human subjects showed total nitrogen to undergo a marked increase, usually greatest on the second day after the anesthesia. These results were confirmed in experiments on dogs and rabbits. His results on the distribution of nitrogen in the urine and the experiments which he made to determine the causes of variations in the different urinary constituents can not be regarded as convincing. His results on sulphur elimination confirmed those of Rudenko, Kast and Mester, and Savelieff.

Paton's[31] recently published series of experiments was directed specifically towards the elucidation of the question of delayed chloroform poisoning. Dogs in a condition of nitrogenous equilibrium were poisoned with chloroform by inhalation, by mouth, and by subcutaneous injection. When given by inhalation for one, two or three hours there was an increase in urinary nitrogen. Changes in ammonia nitrogen were not constant, creatinin excretion was parallel with total nitrogen, and sulphur was not changed. When twenty grams of chloroform were given by mouth on two consecutive days greater changes were produced. He considers that these experiments show a direct toxic action on the liver, and believes that the greater metabolic toxicity of chloroform given by mouth indicates that if chloroform given by the lungs is not eliminated with normal rapidity serious in-

juries might be effected which would lead to symptoms of late chloroform poisoning. He suggests that delayed eliminations occurred in his experiments in which chloroform was given by mouth, because of unusually firm fixation of chloroform by the proteids of the tissues. He expressed the belief that late chloroform poisoning may arise as the result of chloroform given by inhalation, if elimination of chloroform by the lungs is delayed owing to respiratory deficiency or to unusually firm fixation of chloroform by the tissues. His hypothesis is not convincing, because the records fail to show that respiratory deficiency is a constant feature in anesthesia, followed by delayed poisoning in man; no suggestion is offered as to the possible nature of an "unusually firm fixation" of chloroform by the tissue proteids, and the experiments of Moore and Roaf[32] show that this fixation is dependent only upon the vapor pressure of chloroform.

Further chemical evidence regarding late chloroform poisoning is furnished by Taylor[33] and by Wells[34] who analyzed livers, obtained at autopsy, from cases in which death was due to this condition. Taylor was able to isolate leucin, tyrosin, and arginin in relatively large amounts. Wells separated histidin, leucin, tyrosin, glycocoll, and glutamic acid.

The experimental results cited lead to the conclusion that a marked increase of protein katabolism is caused by the action of chloroform upon the tissues, which is independent of the narcotic properties of the substance. The increased katabolism persists for a relatively long time after the administration of chloroform. When chloroform is given by mouth, its effect upon metabolism is more intense than when given by inhalation. It is logical to believe that this fact is due to the greater concentration in which chloroform reaches the liver when given by this path.

It is a striking fact that in none of the experiments upon which these conclusions are based had late poisoning actually been produced. In the papers in which attention has been directed towards this condition it is assumed that a mere intensification of the observed effects of chloroform will lead to the condition of late poisoning. Direct evidence concerning the na-

ture of the condition is necessary in testing the truth of this assumption. The observations that necrotic changes in the liver may constantly be found after chloroform anesthesia in dogs, and that dogs severely poisoned may die from the late effects of the anesthetic, led us to the hope that by producing the condition experimentally, by studying the morphological changes and the urinary excretions, and by comparing these results with those similarly obtained in animals in which recovery from severe poisoning was normal, we could discover in what respects the phenomena of late poisoning are to be differentiated from those of a normal anesthesia.

We have succeeded in making such a study in two dogs in which fatal late poisoning was developed, and in one dog in which severe poisoning, followed by normal recovery, occurred.

I shall give only a brief résumé of the experiments.

Metabolism Experiments.

Methods: The animals used were dogs. On account of the frequency with which vomiting occurs after anesthesia with chloroform, no food was given during any of the experiments. Osterberg and Wolf[35] and Underhill and Kleiner[36] have shown that the metabolism of fasting dogs is practically constant from a day or two after the beginning of starvation, for many days. Water was given *ad libitum*. Most of the urine was collected by catheter. In none of the experiments was there evidence of an infection of the bladder.

Chloroform (Squibbs', for anesthesia) was administered by an open cone, and enough was given to produce and maintain surgical anesthesia. The actual amounts of chloroform used and the percentage strengths of the chloroform inhaled were not estimated.

Total nitrogen was estimated by the Kjeldâhl method; urea, ammonia, creatinin, and creatin by the methods of Folin. The different forms of su'phur were estimated as barium sulphate following the procedures recommended by Folin.

Description of Experiments.

Experiment 1.

White Bull-bitch Pup.

Normal period, June 11 and 12. Chloroform administered on June 13, for two hours in the morning and for an hour and a half in the afternoon. Total period of anesthesia, three hours and a half. Recovery from both anesthesias was normal. The following morning the animal appeared normal except for weakness and general depression. No vomiting occurred.

During the after period, June 14 to 16, no noteworthy symptoms occurred. There was no vomiting.

At the end of the experiment, the animal, apparently perfectly well, was killed with ether, and the autopsy perfomed immediately.

Autopsy: Animal much emaciated. Heart and lungs, stomach and intestines, pancreas and spleen, appeared normal. Liver apparently of normal size; surface smooth; consistency about normal; color strikingly yellow; cut sections showed lobulations plainly; centers of lobules appeared grayish and periphery very yellow. No congestion. Kidneys were of normal size and consistency; surface normal.

Microscopical Examination. Liver: This is very fatty. The fat is chiefly, but not entirely, confined to the periphery of the lobules. Stained with hematoxylin and eosin, it is seen that around the interlobular space in the periphery of the lobule the liver cells retain well their form and staining properties. In the intermediary and central zones great changes have taken place. The liver cells are in all stages of degeneration. Some show only a faintly staining nucleus and the reticular structure of the cell; in others both the nucleus and the protoplasm stain very badly. Other cells consist only of a shrunken and distorted and deeply staining nucleus surrounded by a very narrow rim of protoplasm. From some intercapillary areas the cells have entirely disappeared. Confined almost entirely to the intermediary and central zones of the lobules are scattered giant cells containing within themselves masses which stain dark blue with hematoxylin. These masses are soluble in dilute acetic acid without the production of gas bubbles, stain black with a dilute solution of nitrate of silver, and are therefore composed of calcium phosphate. Only in a few instances are they found among the apparently healthy cells. The number of these in each lobule varies between ten and fifty. The capillaries in the central zones contain a few red blood cells. There are no thromboses.

Kidneys: There is a moderate fatty deposit (not much more than is ordinarily found in dogs) in the cells of the limbs of Henle's loop and in the collecting tubules. The glomeruli are normal. There is a marked degenerative change in the cells of the tubules, especially of the convoluted tubules. Many tubules contain fragments of cells and casts.

Heart: The muscle retains its transverse striations.

Gastrointestinal tract: Normal.

Experiment 2.

FULL GROWN FOX TERRIER BITCH.

Normal period, June 23 and 24. Chloroform administered on June 25. The administration of chloroform was begun at 9:38 a. m., and continued until 12:08 p. m. Chloroform was again given from 4:10 to 6:10 p. m. Total duration of anesthesia, four and one-half hours. Recovery from the effects of the anesthesias was slow but uneventful.

After period, June 26 to 28. Vomiting occurred after water was taken on June 26. No vomiting occurred on June 27 and June 28. Feces containing old blood were passed on June 27.

Second chloroform day, June 29. Chloroform was administered for one and a half hours in the morning, and again for one and a half hours in the afternoon. Total duration of anesthesia, three hours. Recovery was slow. On the following morning, at 7:30 a. m., the animal could stand and walk about, and except for weakness and general depression appeared to be normal in her behavior. From 8:30 a. m., until death occurred at about 10 a. m., she was completely prostrated, and during this time frequent convulsions occurred. They began with increase in depth and frequency of respiration, twitching, and rigidity of the neck muscles; then followed clonic spasms of the legs, and finally a tetanic condition of the whole body. In the intervals between the convulsions prostration was very great, and the animal was unconscious; but the reflexes were retained. During this time black fluid feces consisting of old blood were passed. Vomitus of a similar character was ejected. Death occurred at 10 a. m.

Autopsy: Made immediately after death. The animal was not greatly emaciated, subcutaneous fat being fairly abundant. Heart and lungs appeared normal. The peritoneum was smooth and glistening. The omentum was congested and in it two small areas of hemorrhage were found. It was dotted here and there with typical fat necroses in all stages of formation; none exceeded 4 mm. in diameter. These necroses were found in the fat surrounding the pancreas, within the pancreas itself, and in the mesentery of the colon. The pancreas was very firm and pale. There was no sign of obstruction in its ducts. The gall bladder was full of greenish bile. The cystic and common ducts were patent. The liver was of normal size and very yellow. On the surface and on a cut section it was dotted with very numerous reddish areas of pin-head size, which were evidently in the center of the lobules. The spleen was normal. The cortex of the kidneys was slightly yellowish in the neighborhood of the pyramids; otherwise the kidneys appeared normal. The stomach contained hemorrhagic material, but the mucosa appeared normal. The whole intestinal tract was full of hemorrhagic material. The mucosa of the entire small intestine was hemorrhagic.

Microscopical Examination. Liver: There is not a normal parenchymatous cell to be found in any of the sections. About the portal spaces are a few small islands of cells that retain their approximate form and staining properties, but are very fatty. There are hemorrhagic areas oc-

cupying the center of the lobules. Within these areas the liver cells are in all stages of dissolution. Many are swollen, their nuclei disintegrated or absent, and stain deep pink with eosin. Others have degenerated to amorphous masses. The remainder of the lobules are composed of swollen cells, of which only the nuclei and the reticular structure of the cell may be seen. Scattered among these hydropic cells are others that stain deep pink and are without nuclei. In the hemorrhagic areas only a few small masses stain red with Scharlach R, while in the periphery most of the cells stain deep red. No thromboses are found.

Kidneys: These contain rather more fat than in Dog 1, but in the same situation. The same changes are to be found in the tubules as in Dog 1.

Pancreas: The substance of the pancreas itself is normal. In the fat immediately surrounding the pancreas and in the omentum and mesentery are small hemorrhages and typical fat necroses.

Heart: Muscular striations are present in the heart muscle.

Gastrointestinal tract: The mucous membrane is congested throughout. In the stomach and large intestine a few hemorrhages are seen; in the small intestine they are almost continuous throughout its whole extent.

Experiment 3.

Young White Bull-bitch.

Normal period, July 4 and 5. Chloroform day, July 6. Chloroform given for three hours in the morning and two and one-half hours in the afternoon. Total duration of anesthesia, five hours and a half.

After period, July 7 and 8. During July 7, vomiting occurred very frequently after water was taken. The vomitus did not contain blood. Feces passed on July 7 contained both fresh and old blood. Aside from weakness and these gastrointestinal symptoms, the animal appeared normal. On July 8, until 4:00 p. m., the animal was conscious and apparently normal except for muscular weakness and gastrointestinal symptoms. She stood or walked with difficulty. Vomiting was frequent; the vomitus contained bloody mucus. At about 4 p. m. she became nearly unconscious. She lay on her side and at intervals whined in a semi-conscious manner, snarling and biting aimlessly at the floor of the cage. The respiration was very rapid, sometimes deep and labored. In the evening, at about 9:30, she was unconscious. Her stupor was interrupted by periods of delirious crying, aimless and unconscious or semi-conscious attempts at biting, and incoordinated muscular movements. Death occurred during the night, and on the following morning she was found in a state of rigor.

Autopsy: Made soon after the death of the animal was discovered. Emaciation was not extreme. Hemorrhagic extravasations were found in the tissues of the mediastinum and pleura. The lungs were normal. The pericardium and epicardium contained hemorrhagic areas. The myocardium was pale. The omentum showed areas of marked congestion and contained a few scattered points of hemorrhage. There were numerous areas of hemorrhage in the mesentery. The liver was apparently somewhat

smaller than normal. Its substance was soft and easily friable. In appearance it resembled that of Dog 2, being very yellow with reddish areas at the center of the lobules. The kidneys were of normal size, the tissues somewhat soft, and the cortex pale in color. The stomach contained bloody material of fluid consistency; its mucosa was slightly congested. The intestines were filled with blackish fluid material, evidently consisting chiefly of blood. An accurate judgment concerning the condition of the intestinal mucosa was difficult on account of post-mortem change, which was considerable.

Microscopical Examination. Liver: This is greatly altered. At the periphery of the lobules the cells stain well, but are very fatty. The inner two-thirds of each lobule are hemorrhagic. In the hemorrhagic area the cells are swollen, stain deeply with eosin, and are without nuclei. Giant cells containing calcium phosphate are present in the hemorrhagic areas, but are confined to their periphery and are not found in the center. No thromboses are to be seen.

Kidneys: These are greatly congested. There are small hemorrhages in the cortex as well as the pyramids, and one or two within the glomeruli themselves. In other respects, the changes are like those that have been described.

A faint reaction for albumin was obtained in the urine of each dog on the days on which chloroform was given. The urine showed a slight reducing power when tested with Fehling's solution on these days. The urine of each dog on the days on which chloroform was administered was highly colored and gave strong reactions for bile pigment. This reaction persisted until the end of the experiment, and in the cases of Dogs 2 and 3 was very intense. Gerhardt's test for diacetic acid and Legal's test for acetone were negative in every urine. Every urine was acid to litmus.

The limits of this paper do not include a consideration of the symptoms exhibited by human cases, but a word in regard to the similarity with them of those observed in our dogs may be allowed.

In the so-called cholemic or adult type of the delayed poisoning, a longer or shorter uneventful period is the rule; and so it was with both of our dogs. With Dog 3 at least forty hours intervened after the anesthetic before untoward symptoms appeared, and during this time it was impossible to detect any difference from the recovery from any severe narcosis.

Human cases become wildly delirious and occasionally have convulsions, and coma ends the scene. The signs of mental disorder or the equivalent of mental disorder in a dog were seen in both of our cases. In Dog 2 there were convulsions, and in Dog 3 purposeless attempts to bite and snarling and howling. Coma supervened in both instances. The vomiting of blood and the bloody stools, and the large amount of bile pigment in the urine are common to both animals and human beings.

Summary of Results.

For the sake of brevity I will summarize the metabolic results of the three dogs. I would like to emphasize again that the first one had recovered so far as the metabolism and symptoms were concerned, and therefore makes an admirable control, while the other two dogs died of delayed poisoning.

First, as to *nitrogen excretion.* All experiments are alike in that they give an increase in katabolized nitrogen on the day of poisoning. On the day *after,* in every experiment, a still greater increase occurred (54 per cent. in Experiment 1; 76 per cent. in Experiment 2; and 185 per cent. in Experiment 3). On the third and fourth days in Experiment 1, a gradual decrease to normal took place. In Experiments 2 and 3, the nitrogen estimation remained high until the end. But the mere total loss of nitrogen alone can not be the cause of death, for an animal can stand very easily the loss of nitrogen shown in these experiments, under simple starvation.

Urea and ammonia. It is surprising to see how closely the excretion of urea nitrogen follows total nitrogen. It is true that on the day after poisoning in each case, there was a diminution in the relative excretion of urea nitrogen; but it was only slight and tended to return again to the former percentage figure. The percentage excretion of urea was always within normal limits. On the day following the poisoning there was a divergence of the urea curve from that of total nitrogen, the percentage decrease was not always compensated for by a percentage increase in the ammonia. There was an actual increase in ammonia nitrogen on

each day on which chloroform was given, but it was not proportional to the increase in total nitrogen, and hence in every case a percentage decrease was found. A greater increase in ammonia nitrogen occurred in every experiment on the day following chloroform, so that in Experiment 2 the percentage returned to normal; and in Experiments 1 and 3 it slightly exceeded normal. In Experiment 3 the percentage again sank, while in Experiment 1, the dog which recovered, it remained high. It is very surprising to see so little change in ammonia; in Experiment 3, the pure delayed poisoning, it was within normal limits throughout.

In human cases there can be no doubt that ammonia nitrogen would be very much increased on account of the diacetic and oxybutyric acids present, but these were entirely absent in our dogs.

The undetermined nitrogen, representing the purins, uric acid and amino acids, increased in each experiment on the day of anesthesia. The percentage on this day was high in all and much above normal in Experiment 2. A still greater absolute increase took place on the day following chloroform, which was enough in Dogs 1 and 2 to make a percentage increase, but not in Dog 3, in which a decrease in percentage value occurred. The fact that there was no greater increase in undetermined nitrogen in the fatally poisoned Dog 3 than in the control tends to lessen the emphasis that might otherwise be laid upon this increase.

Our figures show that if the increased nitrogenous excretion is due to autolysis, this may occur to an abnormal degree without causing great abnormalities in the distribution of nitrogen as urea, ammonia, and amino acids. Leucin and tyrosin were never found in the urine of these cases, but these have been missed in many cases of phosphorus poisoning, and there is no *a priori* reasoning why after chloroform poisoning the enzymes that split off ammonia from amino acids and convert it into urea should not still be active.

Creatin and creatinin. In Experiments 1 and 2 the absolute values for creatinin were almost constant throughout, an-

other instance in which this excretion may be unchanged even when large amounts of tissue protein are being decomposed. In Experiment 3 creatinin was constant on the two normal days and the chloroform day. It disappeared altogether on the day following anesthesia, but reappeared in small amount on the final day. These changes produced a marked decrease in the percentage values. The creatin was increased in every experiment on the day of chloroforming, and still more so on the following day. In Experiment 1 it returned to normal, but remained high in the other two experiments and continued to rise in Experiment 3, so as to be on the day of death more than three times the amount it was in health. With the present uncertainty as to the origin and indications of creatinin and creatin, it would be hazardous to draw conclusions. The greatly increased creatin undoubtedly has its source, as Benedict, Shaffer, and Mellanby believe, in the creatin of the muscles when rapid loss of muscle protein is going on, which is certainly the case after chloroform. The possibility must be borne in mind that the chloroform may have interfered with the formation of creatinin, and our figures may be considered as supporting in a measure the view of Mellanby that the liver is the organ chiefly concerned in the formation of creatinin.

Total sulphur. On the day of chloroform poisoning in each experiment, the increase in neutral sulphur was greater than the increase in sulphate sulphur. On the day following chloroform in Experiment 1, recovery of the normal sulphur relations began. In Experiment 2, a decrease in sulphate sulphur occurred while neutral sulphur underwent a still further increase. In Experiment 3, on this day, both increased. The second day of chloroform in Dog 2 was marked by changes in the sulphur excretion similar to those on the first chloroform day. It is obvious that we have not only a great increase in the amount of total sulphur, but a disturbance in the percentage distribution. It is interesting to compare the excretion of total sulphur to total nitrogen during the normal and poison days.

In Experiment 1, on the day of poisoning and the three

succeeding days, nitrogen equivalent to five and one-half normal days was excreted, but sulphur equivalent to six and one-third days.

In Experiment 2, in five days the equivalent of eight and one-sixth days nitrogen was excreted, but sulphur equivalent to eleven days.

In Experiment 3, in three days, seven and one-half days nitrogen was excreted and more than eight days sulphur.

All of this points to the fact that protein richer in sulphur is being katabolized in fasting. This has been found with other severe poisons. While it is constant immediately after chloroform in each instance, and was repeated in Experiment 2, the effect was no more prolonged or intense in the fatally poisoned Dog 3 than in the control.

We conclude from Experiment 1, the dog which recovered, that anesthesia with chloroform produces a very great increase in total nitrogen elimination, but that with the exception of creatin and creatinin the so-called partition of nitrogen-containing substances is normal. The sulphur excretion is also greatly increased and is carried out in an abnormal ratio. We see further from an analysis of the figures of Dogs 2 and 3, which died of delayed poisoning, that they differ from Dog 1 only in the degree and duration of the nitrogen excretion. They, too, with the exception of creatin and creatinin partitioned their nitrogen-containing substances in a normal manner, and Dog 1 exhibited the same abnormalities in the excretion of sulphur as Dog 3.

We are led to believe, therefore, that the metabolic differences between ordinary prolonged anesthesia and delayed poisoning are of degree only, and not of kind. We find further no basis for the widely disseminated view that cases of delayed poisoning are due to acid intoxication.

Pathological Results.

From our experiments and those of others, it is plain that a single anesthesia with chloroform, of a duration of more than half an hour, induces fatty changes. These are demonstrable in

the liver in from twelve to twenty-four hours, reach their maximum in about forty-eight hours, and then gradually retrograde; but the excess of fat may be demonstrated for about two weeks. The fat appears first in central and intermediary zones of the lobule, and eventually may spread to the periphery and the whole lobule be intensely fatty. With more prolonged, and especially with repeated anesthesias, which are very much more destructive than single ones, necrosis appears. But, as is shown by two of our experiments, anesthesia of only one or two hours is sufficient, at least at times, to cause necrosis. The necrosis also begins in the center and extends centrifugally, so that almost all the cells may be necrotic and only a few around the portal spaces be still living.

The amount of protoplasm in the necrotic cells varies according to the length of time intervening before death. When this occurs promptly the cells may remain of almost normal size and contour. When longer delayed, the protoplasm diminishes markedly until there may be only the narrowest margin around degenerated nuclei which lie in the intercapillary spaces. The amount of hemorrhagic extravasation varies from none at all to a very considerable amount.

Very striking in two of our metabolism dogs were the calcium deposits and the giant cells surrounding them. These deposits were always in the necrotic areas and chiefly in the periphery of these. Their presence in less than forty-eight hours after poisoning indicates the rapidity of calcium deposition and engulfing cell formation. There is no mention of such deposits in pathological or experimental literature relating to chloroform. That they follow as a result of the chloroform is shown by the fact that we produced them in two instances.

In our second metabolism experiment mention was made of fat necrosis of the omentum and mesentery. There is no similar record in the literature. That fat necrosis sometimes occurs with hepatic poisons is shown by the reported observation of Wells[37] in regard to hydrazine poisoning. He produced in one dog small and scattered but typical fat necroses. Our result with choloroform stands as an isolated observation.

The changes produced in the kidneys and heart have been found, by other investigators and by ourselves, to be much less constant and severe than in the liver. From our experience it seems that there is not enough damage usually done to these organs to explain an interference with this functional activity.

We have found congestion and small areas of hemorrhage in the gastrointestinal tract frequently, and in one dog the whole small intestine was hemorrhagic. In this same dog were hemorrhages into the peritoneum, pleurae, pericardium, and mediastinal tissue. We have also found hemorrhages in the serous membranes of other dogs. The lesions found elsewhere are negligible.

It may thus be seen that there is a very great similarity between the human and the experimental lesions. In both they are most severe in the liver and consist of central necrosis and fatty degeneration, and, allowing for a certain difference in structure of the organ, are strictly comparable. The same may be said of the kidney lesions. In both of these there is also a tendency to hemorrhage into the serous membranes and into the gastrointestinal tract.

We have previously said that, from our metabolism studies, we were led to believe that the differences between the changes produced by prolonged anesthesia, and those produced by delayed poisoning, were of degree and not of kind. This view is strongly substantiated by the pathological examination. Dog 1, which was recovering and which served as a control, had changes exactly similar to those in Dog 3, but they were not so severe. That in this Dog 1, with the extensive liver lesions, the metabolism should have been normal at the close is remarkable and serves to show that metabolism may not be disturbed even by severe organic lesions in the liver.

Furthermore, the many experiments which we have made show unmistakably that any prolonged anesthesia with chloroform produces in the dog great alterations and even destruction in liver tissue, although there may be apparent perfect health. We believe that this is true of human beings as well as of animals.

REFERENCES.

[1]Casper: *Woch. f. d. ges. Heilkunde*, 1850, xvi, 1, 17, 33, 49, 273.

[2]Langenbeck: *Behrend's Chlorof. Statistik*, Hanover, 1850.

[3]Mouat: *Med. Times and Gazette*, 1856, ii, 225.

[4]Thiem and Fischer: *Deut. med. Zeitung*, 1889, x, 1111.

[5]Bastianelli: *Bull. d. osped. di Roma*, 1891, x, 179.

[6]Fränkel: *Virchows Archiv*, 1892, cxxix, 254.

[7]Ambrosius: *Virchows Archiv*, 1894, cxxxviii, Suppl. Heft.

[8]Guthrie: *Lancet*, 1894, i, 193, 257.

[9]Bandler: *Mitteil. a. d. Grenzgebieten d. med. u. Chirur.*, 1896, i, 303.

[10]Marthen: *Berl. klin. Woch.*, 1896, 204.

[11]Heintz: *Inaug. Diss.*, Rotterdam, 1896.

[12]Steinthal: *Jahrbuch f. Chiru.*, 1896.

[13]Brewer: *Annals of Surgery*, 1902, xxxvi, 481.

[14]Bevan and Favill: *Jour. Amer. Med. Assn.*, 1905, xlv, 691.

[15]Holmes: *Appendicitis*, p. 215.

[16]Cushing: *Jour. Amer. Med. Assn.*, 1906, xlvii, 1191.

[17]Ballin: *Annals of Surgery*, 1903.

[18]Wells: *Jour. Amer. Med. Assn.*, 1906, xlvi, 341.

[19]Guthrie: *Lancet*, 1903, ii, 10.

[20]Nothnagel: *loc. cit.*

[21]Ungar: *Vierteljahr. f. ger. Med.*, 1887, xlvii, 98. Junkers: *Inaug. Diss.*, Bonn, 1883.

[22]Ostertag: *Virchows Archiv*, 1889, cxviii, 250.

[23]Strassmann: *Virchows Archiv*, 1889, cxv, 1.

[24]Thiem and Fischer: *loc. cit.*

[25]Bandler: *loc. cit.*

[26]Heintz: *loc. cit.*

[27]Offergeld: *Arch. f. klin. Chirurgie*, 1905, lxxv, 758.

[28]Strassmann: *loc. cit.*

[29]Kast and Mester: *Zeit. f. klin. Med.*, 1891, xviii, 469.

[30]Vidal: *Thèse de Paris*, 1897.

[31]Paton: *Proc. of the Royal Soc. of Edinburgh*, 1908, xxviii, 472.

[32]Moore and Roaf: *Proc. of the Royal Soc. of Edinburgh*, 1904, lxxiii, 383, and 1905, lxxvii, 86.

[33]Taylor: *Univ. of Calif. Publ., Pathology*, 1904, i, 43.

[34]Wells: *Jour. Biol. Chemistry*, 1908, v, 129.

[35]Osterberg and Wolf: *Biochem. Zeit.*, 1907, v, 304.

[36]Underhill and Kleiner: *Jour. Biol. Chemistry*, 1908, iv, 165.

[37]Wells: *Jour. Exper. Med.*, 1907, ix, 627.

Discussion.

Dr. George E. Brewer, in discussing the clinical aspects of delayed chloroform poisoning, said that he considered these important for two reasons: First, because the disease itself is such a frightful one and the death-rate is so high; and, second, because its symptomatology is not generally understood, the cases being so exceedingly rare. As regarded the symptomatology, after a review of the literature, the cases could be classified under three general heads. 1. The type of disease generally seen in children and described by a certain number of authors, in which symptoms come on almost immediately and are associated with a profound degree of shock, the chief symptoms being prolonged vomiting, great prostration, coma, and death. In a certain number of cases acetone is found, but this is rare. High temperature may also be a symptom. 2. Another class of cases seen in children shows distinctly evidences of delayed poisoning. This class could best be illustrated by the history of one of Dr. Brewer's patients, a child about twelve years of age, with acute appendicitis, operated upon at the Roosevelt Hospital. The appendix was gangrenous and was surrounded by pus. There was limited peritonitis. The operation was short; chloroform was used; the patient was on the table for twenty minutes. He recovered from the anesthetic quickly. During the night he was comparatively restless; but there was then a drop in temperature, and he had a comparatively favorable day. The bowels moved; there was little vomiting. On the third day he seemed to be entirely convalescent. Urine was secreted freely. The mind was clear; and the child was hungry. He went to sleep in the early evening, and at twelve o'clock woke suddenly with a piercing scream. He looked about in a dazed condition, did not recognize anyone, and suddenly dropped into sleep again. In the morning he awoke again in the same way with a terrific shriek, evidently of abject terror and fright. He failed to recognize anyone and dropped into sleep again. This was repeated all day about every fifteen minutes or half hour. At night it was perfectly evident that the

child was in a very serious condition. There was a very decided odor of acetone in the breath, and the urine showed acetone and diacetic acid. During the following night the sleep deepened into profound coma, and the child died the following morning. In this case there was no vomiting and no fever. The chief symptoms were extreme restlessness, delirium of the wildest sort, gradually deepening coma, and a rise of temperature before death. On further investigation the child was found to be simply loaded with acetone and diacetic acid. This was the second type of cases, and represented the most frightful clinical picture which he had ever seen. 3. A third type of cases, Dr. Brewer had seen well illustrated in a patient, a man of fifty-six years, who had a moderate appendicitis. The operation was comparatively easy and short; and the patient took chloroform because of some damage to the kidneys. He did perfectly well for forty-eight hours; all symptoms disappeared; and he was considered thoroughly convalescent, when he suddenly became somnolent. When he woke up he seemed somewhat dazed. On the third day icterus appeared, and on the fourth day he was the color of an orange. The sleepiness increased to coma, and he died. An autopsy was fortunately obtained. The liver was rather small and very yellow. Almost no normal liver cells remained.

In reviewing the clinical histories of these cases, about ten or a dozen symptoms could be described, some of which appeared in all cases, some in only a few. Vomiting was quite generally present. Restlessness was almost invariably present in the beginning. The delirium was of the wildest sort, denoting great terror, and had been described as the delirium of delirium tremens by some authors. Icterus was sometimes present and sometimes absent. Coma was always the end, progressively deepening. Fever was not usually present, although in a few cases it had been exceedingly high, as high as 170° directly after operation. Cyanosis, air hunger, and dyspnea had been present in a certain number of cases, but were not symptoms to be relied upon. In the first class, where there were evidences of shock, it might be that there were other elements also present. But when

we consider late chloroform poisoning we must look for vomiting, restlessness, wild delirium, and coma. Acetone might or might not be present; when it was, it was usually associated with severe delirium. Since seeing his first case, Dr. Brewer had seen a few milder cases in which the patients were somnolent, with acetone in the urine, which then cleared up. He could recall three such cases. The severer cases almost invariably ended in death.

Dr. James Ewing said that he had been told that when chloroform was first introduced Magendie declined to use it because he did not know what might happen after recovery from the anesthesia. Of course, such a precaution was ignored, and he had few or no followers; but the subsequent history has justified his scientific caution. Dr. Ewing thought that it was remarkable that, in spite of the fact that clinicians have been warned of the dangerous delayed action of chloroform, they have paid little attention to this condition. In England, especially, where one commission for the study of chloroform had been succeeded by another, and where Guthrie was repeating his warnings, there least of all was attention paid to this form of delayed chloroform poisoning. In France, in 1905, so-called cases of toxic appendicitis were described. The authors gave pictures of the lesions in the liver which were identical with the pictures shown by Dr. Howland. The clinical history of the three cases which they reported was identical with that described by Drs. Howland and Brewer, though the authors make no mention of such an explanation. These authors referred to Dieulafoy for corroboration of their views, but the evidence which they gave showed only that they were dealing with delayed chloroform poisoning. They quoted from half a dozen surgeons of France, each of whom had reported similar cases. In one case the diagnosis of hystero-epilepsy was made. The worst offenders in this field were the obstetricians, and though the warning had been sounded again and again, it had had very little effect upon the free use of chloroform. Dr. Ewing thought a considerable proportion of cases of toxemia of pregnancy were cases of delayed chloroform poisoning. He differed from Dr. Brewer

in regard to the frequency of the disease. He had no difficulty in finding material showing the lesions. He thought the condition was relatively common. The cases were seen at autopsy probably in larger numbers than were recognized in the wards. He had been much interested in the pathological anatomy shown in the sections. He thought possibly some information might be gained by a study of the nervous system in these cases. No doubt there were some observations of this sort, but he was not familiar with them. The important question was to what extent these observations made on dogs were applicable to man. It seemed certain that the dog was more susceptible to these lesions than was the rabbit. He had not been able to produce in the rabbit any such necrotic lesions as Dr. Howland had produced in the dog. Whether man is as susceptible as the dog or not, is not known. So far as the clinical course was concerned, the symptoms in dogs were reproduced in man as perfectly as one could demand. When the organs were examined the evidence was indisputable that exactly the same thing happened in man as happened in the lower animal. It was, therefore, justifiable to conclude that the toxic effects observed in the dog occur regularly and in the same way in man, though he thought caution should be used in attributing all such lesions to chloroform poisoning. These lesions could arise spontaneously without chloroform. If man were normally less susceptible than the dog, there was no question that the conditions which arise in man during which an anesthesia is used, render him much more susceptible. So that it is perfectly clear that the bearing of the previous condition of the patient on the choice of an anesthetic is most important. He had himself been most interested in the results of the metabolic studies, and had been surprised to find that there was so little change in the nitrogen, when according to the autopsy the liver was almost completely destroyed. He had this general objection to comparing the results of metabolism studies in dogs with the conditions which are met with clinically: One takes a dog in normal condition, and by administering chloroform rapidly produces severe lesions in the liver; and then one makes examinations of the urine and discovers that in

urine collected during the time in which the animal lives there is no change in the nitrogen; and he concludes that such changes can arise spontaneously without producing any change in nitrogen partition. This conclusion was, he thought, quite unwarranted. The metabolism in spontaneous diseases in which these marked lesions were found could not be deduced from observations of previously normal animals in which such lesions were rapidly produced by experimental methods of this sort. It was quite possible that in some of these cases the extreme destruction of the liver substance occurred only during the last few hours of life. Yet cases of acute yellow atrophy had been observed in which there was almost nothing left of the liver, in which the nitrogen showed very little alteration. The most important question connected with this work, it seemed to him, was the present status of chloroform. What is the case against chloroform? It seemed to be perfectly clear, and yet although it had been clear for years it needed iteration and reiteration, and such striking evidences as Dr. Howland had given, and especially such careful metabolism work as he and Dr. Richards had done.

Dr. C. G. L. Wolf: Through the kindness of Dr. Howland, I have had the privilege of going over the results in the metabolism in delayed chloroform poisoning which he has presented; and while it may appear at first sight that the analytical results do not present changes commensurate with a fatal outcome, it seems to me that they are particularly instructive, in view of the direction which urine analysis has tended to take in the last few years. Instead of the routine analysis for urea by the hypobromite method, an accurate knowledge of the distribution of nitrogen is now desired, and this is given in the form of results similar to those of Dr. Howland. To what extent do Dr. Howland's results support this type of analysis? Dr. Howland finds in delayed chloroform poisoning: 1. That the liver, the principal gland involved in processes leading to metabolic changes which are represented in the urine by the formation of urea, is altered to such a degree that, microscopically, practically no cells with a capacity for functionating can be detected; 2.

That the results of the analyses by the methods to which I gave the name "nitrogen and sulphur partition" show a practically normal urine, although there is an obvious toxic destruction as shown by the nitrogen elimination.

If this be the case, we are confronted with a very serious question regarding the utility of this type of analysis for the purpose of diagnosis.

In the course of work to which my entire attention has been directed during the past four or five years, I have come across many conditions which bear out Dr. Howland's results in every detail. The first was brombenzol poisoning, a condition in many respects similar to cystinuria. In this toxic condition the liver is most profoundly changed, and yet the urine, with the exception of certain features, is not at all changed commensurately with the degree of liver destruction. The results were so anomalous that I decided, before publishing my conclusions, to take up normal metabolism as affected by different diets solely, and this investigation, part of which has been published, part of which is completed, but still unpublished, has taken over two years, and the work is by no means finished. I mention these details merely to show that it is absolutely necessary, before nitrogen partition can be used for diagnostic purposes, that the whole field of normal metabolism, as affected by diet and by the state of nutrition of the individual, be carefully investigated. This, so far, has not been done.

During the course of the work on normal metabolism I have investigated a number of other conditions which bear on this problem of the relation which the microscopical changes in the liver bear to the urinary findings. I have modified Lieblein's original experiment, in that I have temporarily clamped the common and cystic ducts, and have injected strong solutions of argyrol under pressure into the hepatic ducts. No change whatever was found in the distribution of nitrogen in the urine. Similarly I have performed a number of experiments with poisoning with carbon monoxid and with hydrocyanic acid, a poison which is believed to affect profoundly all katabolic activities,

without observing any change in the nitrogen partition. Lastly, in chloral hydrate intoxication leading to the death of the animal, the results, in so far as a general consideration of the nitrogen and sulphur analyses go, show that the poison is also without effect.

On the other hand, I have been able to produce very remarkable changes in the nitrogen and sulphur partition merely by the administration of suitable diets. These changes are greater than any I have found in the toxic states above mentioned, or in those which Dr. Howland has presented. It is pertinent, therefore, to ask what bearing these facts have on the general problem of urine analysis as applied to the diagnosis of changes in the liver, such as those that Dr. Howland has brought about by delayed chloroform poisoning.

In 1906 and 1907 Ewing and I published two papers on the clinical significance of the urinary nitrogen, as applied more particularly to the examination and diagnosis of conditions such as the toxemia of pregnancy, in which the liver on microscopical examination shows changes somewhat comparable to those found in chloroform poisoning. The main feature of this investigation was that changes in the distribution of the nitrogen were indicative of changes in the organs leading to the formation of the end products of metabolism. There were laid down certain standards for the distribution of the nitrogen, outside of which findings might be considered pathological.

I have not assured myself that the method as generally used has given altogether satisfactory results. The reason for this is a consideration of results similar to those of Dr. Howland, and the further conclusion that much more information must be available on the behavior of normal persons on restricted diets and with different states of nutrition.

By reason of the technical difficulties in procuring subjects for such investigations, I have been obliged to experiment with animals; but the results which I have thus obtained have convinced me of the necessity for a complete investigation of normal metabolism in undernutrition, before the method of nitro-

gen partition can be used for the purposes of accurate diagnosis. Work which I have finished on the hourly excretion of urine has shown that it is possible to obtain from the same subject, on the same day, samples of urine simply astonishing in their differences in composition; and that the change from one composition to another takes place with the greatest rapidity.

I have spoken first of the negative results of Dr. Howland's investigation. I wish now to call attention to certain positive results which he has obtained which seem to be of great interest.

In a Harvey lecture given about a year ago, Folin emphasized a direction which he considered was of the highest importance for investigation into pathological metabolism. This was the study of those processes which are connected with the essential carrying out of protein metabolism, quite apart from any question of food intake. To this type of metabolism the name "nitrogenous" has been given. One of these processes apparently leads to the formation of creatinin; and if creatinin be absent, one would conclude that this function, an essential one for the organism, has been abolished. In one of the cases which Dr. Howland has presented, creatinin is shown, for the first time in any urine so far as my knowledge goes, to be absent. I should conclude from this a very profound disturbance, probably irrecoverable, as a result of chloroform poisoning. In all his cases there is a marked diminution in the amount of creatinin eliminated, as a result of the toxic process.

This is one of the constant results which I have met with in brombenzol, hydrocyanic acid, carbon monoxid, and chloral hydrate intoxications, and has also been seen by Shaffer and others in certain pathological conditions in man. That it is not due simply to starvation I can show by a comparison of a number of experiments which I have made with normal fasting animals, and we must accept the low creatinin in Dr. Howland's results as a distinctly pathological indication of importance.

With regard to the rise in creatin, we have also, as Folin pointed out, an index which is probably of great significance. In my fasting animals which have been mentioned, creatin appears

on the third or fourth day, depending probably on the condition of nutrition of the animals. With, however, the administration of brombenzol, hydrocyanic acids, carbon monoxid, or chloral hydrate, the excretion of creatin is increased far beyond anything I have ever observed in fasting. On the other hand, I have never found the most unusual amounts of creatin which Dr. Howland has obtained, and I conclude, therefore, that the process of chloroform poisoning is one of most severe character on this account.

I have not taken up the distribution of sulphur, nor its importance in diagnosis. The matter seems to me at present much too obscure to use as a basis for diagnostic work, as Zweifel has attempted. It is, however, interesting, as Dr. Howland has pointed out, that the type of protein attacked is one containing a large proportion of sulphur. This I have found in brombenzol poisoning and in hydrocyanic acid. That a protein of this kind is very important for the individual is shown in undernutrition. Here I have found that while the animal parts with its nitrogen readily, it seeks to protect its sulphur, so that during a period of undernutrition much more nitrogen is lost than sulphur. Precisely the opposite occurs in chloroform poisoning, hence the toxic action of the drug. The important high sulphur protein is katabolized, and this most probably increases the poisonous effect of the anesthetic.

Dr. E. Libman said that he thought the Societies should be very much pleased with the opportunity which they had had to listen to so valuable a paper, both because the subject had been so well worked up, and because it was an unusually good subject for a joint meeting. He agreed with Dr. Ewing that these cases were not infrequent, particularly the milder forms. Of course, the danger now would be that everything would be attributed to chloroform poisoning, but at any rate it was clear that there was great danger in using chloroform. He wished to record his impression that alcoholics were more likely to suffer from delayed chloroform poisoning.

A CASE OF CONGENITAL FALSE DIAPHRAGMATIC HERNIA.

H. S. MARTLAND, M.D.

The specimens which I have to show comprise the thoracic viscera of a man who died as the result of a congenital deficiency in the central tendon of the diaphragm, which opening connected directly with the pericardial cavity, the heart at autopsy being surrounded by the entire transverse colon, with the great omentum and the greater part of the splenic and hepatic flexures of the gut.

The patient was a man, seventy years of age, who was admitted to the Newark City Hospital in December, 1908, suffering from intense dyspnea, which he had had for about one week. His family and personal history, except for the fact that he was never confined to his bed on account of sickness, had no bearing on the condition to be described.

On admission, the patient presented the clinical picture of an acute right heart dilatation, being markedly cyanotic and dyspneic, with rapid, irregular, and feeble pulse. Aside from these symptoms, there was little in his physical examination which was of interest.

The apical cardiac impulse could not be seen nor felt, but was heard best in the sixth intercostal space in the left mid-clavicular line. The heart sounds were weak and distant, no murmurs being heard. Examination of the lungs revealed crepitant and subcrepitant rales in both infraclavicular spaces, and large moist rales over both bases posteriorly. The abdomen was negative. Examination of the urine showed a moderate amount of albumin, a few small hyalin and granular casts, and a specific gravity of 1.016.

The treatment consisted of the usual cardiac stimulants, but the patient's condition did not improve and he died seventeen hours after admission.

On autopsy the condition shown in the photograph was found. On opening the abdomen, the small intestine occupied

the usual position. The serosa showed in three places, at intervals of about 20 to 30 cm., large injected vessels and a reddened and thickened peritoneum. These areas were practically all in the jejunum, and were thought to be areas of chronic hemorrhagic peritonitis. The transverse colon and great omentum were conspicuous by their absence. The rest of the abdominal viscera were all in their normal positions.

The right dome of the diaphragm reached the fourth interspace, the left was opposite the fifth rib. Just above the left lobe of the liver, the hand could be passed through a large oval opening, 4 x 5 cm. in diameter, directly into the pericardial cavity, where the heart was felt surrounded by the distended transverse colon and the great omentum. On gently dragging on the splenic flexure of the colon, the hernia could be easily reduced as far as the middle of the transverse mesocolon, where there was a small area of gastrocolic omentum adherent to the right free edge of the opening.

The stomach was in the abdominal cavity, somewhat

turned, a portion of its posterior surface presenting, the greater curvature just entering the hernial opening.

On opening the pericardium, the parietal layer was diffusely but only moderately thickened. The right heart was dilated; the left ventricle was firmly contracted. The hernial opening presented rounded borders, and the peritoneum of the under surface of the diaphragm was continuous with the parietal pericardium. There was no hernial sac; nor was any evidence found of a former suppurative pericarditis, empyema of the pleural cavities, suppurative hepatitis, subphrenic abscess, ulcer of the stomach, or neoplastic growth near the diaphragm.

The remainder of the autopsy showed only the ordinary visceral changes of senility. The left adrenal, however, presented a cortical adenoma, about 25 mm. in diameter. It was concluded, therefore, that death was due to cardiac embarrassment, due either to a slipping of too large a portion of intestine, or to gaseous dilatation of the same, through a congenital deficiency of the diaphragm in this position. From the chronic inflammation seen in the small intestine, it seemed probable that this portion also had at times slipped through the hernial opening.

An explanation of this congenital deficiency upon an embryological basis was rather difficult, although it might be included under the theory of diaphragmatic hernia in general; namely, that the partition subdividing the primitive body cavity into pleuro-pericardial and peritoneal compartments is completed by fusion of segments (septum transversum, pillars of Uskow) which for a time are separate; arrested development or delayed union therefore results in abnormal clefts, and it is evident that various degrees of developmental arrest or delayed union may produce corresponding imperfections in the future diaphragm. In this case such an arrest probably took place at about the fifth or sixth week of embryonal life. It was probable also that this was a teratological rather than an embryonal fault, and one which was closely allied to a beginning subthoracic ectopia cordis.

ON THE VALUE OF THE USE OF AMMONIUM OXALATE IN BLOOD CULTURE TECHNIQUE.

CHARLES RYTTENBERG, M.D.

The value of blood cultures as a diagnostic method has become more and more evident in recent years. With the progress of investigations along this line, it has been found necessary to use different methods for different types of cases, and in the course of the work a large variety of media has been introduced. In the ordinary blood culture it is often advisable to use four or more media.[1] In hospitals it is easier to use a variety of media, but in private practice this is not so simple. Epstein[2] suggests the use of ammonium oxalate in blood culture work for the purpose of preventing coagulation of the blood, so that the use of elaborate media at the bedside could be dispensed with and a number of methods could be employed with the blood culture after it had reached the laboratory. He pointed out in his paper that, apart from this advantage, it allowed of a more careful distribution of the blood in the various media. It has been the experience of all investigators who have made blood culture studies, that it is difficult to distribute rapidly and properly in various media blood that is on the point of coagulation. He also pointed out that the coagulation of the blood adds to the bactericidal action of the serum. Chantemesse, in his work on typhoid blood cultures, reported the use of sodium citrate to prevent coagulation of the blood. Two months before the issue of the paper by Chantemesse, the ammonium oxalate method was introduced into our laboratory.

It is evident that there is an additional advantage in the use of ammonium oxalate, in that the blood can be obtained from the patient by a person who is not thoroughly conversant with bacteriological technique. And it is also an advantage in private practice to have a method which prevents as much as possible the alarm of the patient or the relatives by the display

[1] LIBMAN: *Johns Hopkins Hosp. Bull.*, July, 1906.
[2] EPSTEIN: *Amer. Jour. of Med. Sciences*, September, 1907.

of a large amount of apparatus. It is apparent that oxalated blood can be centrifugalized, and that spreads can then be made from the sediment and examined microscopically for bacteria in intense infections. The supernatant fluid can be employed for the determination of the opsonic index.

In the *Mount Sinai Hospital Reports*, Volume V, I have already given our experience with the use of ammonium oxalate solution in ninety cases. In the present paper I shall give the result of our studies up to March 15 of the past year. The present series includes the cases given in the previous paper.

The following reagent, devised by Epstein, has been employed in our investigations:

Ammonium oxalate, 2 gms.
Sodium chloride, 6 gms.
Aq. dest., 1,000 c. c.

The resulting solution is distributed into large test tubes in quantities of ten c. c. (measured accurately by means of a pipette or measuring funnel), and sterilized for twenty minutes on each of three successive days. It can be seen by referring to the formula that this is an isotonic solution, for it contains 0.6 per cent. sodium chloride. The level of the fluid is indicated on the tube by a blue pencil mark, which serves as a control over evaporation and shows at a glance the approximate amount of dilution of the blood after it has been added to the solution. The tubes are then stored in the ice-box until they are needed. The oxalate solution should never be used immediately after being taken from the ice-box, but should be allowed to stand at room temperature for some time, or gently warmed. The cold solution might exert a detrimental effect on the organism sought, and by eliminating this factor, the chances of a negative result are diminished. Our experience has shown us that a fresh solution is preferable, so that our stock is renewed every third or fourth week.

Briefly stated, the action of the oxalate is as follows: It precipitates the calcium salts of the blood in the form of calcium oxalate, thereby preventing the coagulation that would

normally occur. In other words, it is a decalcifying agent, and by removing the calcium base the fibrin ferment of the withdrawn blood is rendered inert, and hence clotting does not take place.

Technique of Obtaining Blood and Preventing Coagulation.—We employ the usual apparatus and method for obtaining the blood, preferably from one of the veins in front of the elbow. In our investigations part of the blood (usually 4 to 8 c. c.) was immediately introduced into the tube of the oxalate solution, after sterilization of the mouth of the tube in the flame of an alcohol lamp. The remainder was distributed in the usual series of media. The 10 c. c. of ammonium oxalate are more than sufficient to decalcify 10 c. c. of blood, which was the maximum amount used in any single case because of the danger of contamination in case the blood oxalate solution came into contact with the cotton plug. Gently oscillating the tube is sufficient to mix the blood thoroughly with the oxalate solution in cases where a moderate amount (2 to 5 c. c.) of blood has been obtained. When 6 to 10 c. c. are introduced into a single tube of the oxalate solution, it has been my technique to pour the mixture into a sterile tube and back again into the original tube with the usual precautions. In this way one can be sure of a more rapid and even distribution of the blood in the oxalate solution, so that all possibility of clotting is obviated, even though the coagulation time of the patient's blood be markedly diminished. On standing, the blood-oxalate solution usually separates into a stratum of blood cells with a supernatant layer of turbid fluid. When later platings are made, it is desirable to pour the mixture into a sterile tube and back again into original tube before adding the oxalated blood to the medium selected. This distributes the cells evenly in the solution, and plates of uniform color are obtained.

Media Used.—In our investigations the routine blood culture set employed in our laboratory was used as a control. This set was introduced by Dr. Libman, and consists in the use of flasks of plain bouillon (1 per cent. acid) and 2 per cent. glu-

cose broth bouillon (1 per cent. acid), together with plates poured from the blood mixed with plain agar (1 per cent. acid), serum agar, 2 per cent. glucose agar, 2 per cent. glucose serum agar, 5 per cent. glycerin agar, and neutral plain agar. Corresponding flasks and plates from the oxalated blood were made from time to time, some at once, others at intervals of thirty minutes, one, two, three, or five hours, etc., depending upon the amount of blood withdrawn. Occasionally we have extended the intervals, plates at times being poured twenty-four to thirty-six hours after the blood had been obtained. In the intervals between plating, the oxalated blood was kept in the thermostat at 37° C.

Results.—Three hundred and twenty-four blood cultures have been taken in which the method has received a fair trial. Of this number, eighty-seven positive cultures are available for study. The blood cultures were made in all the usual types of disease encountered in hospital work. The following is a short list of the diseases in which the positive results were obtained: Typhoid fever, pneumonia, post-partum infections, pyelitis, pyosalpinx, infectious endocarditis, otitic infections, erysipelas, local infections in various parts of the body, abscesses of various parts of the body, gall-bladder infections, osteomyelitis of various bones, glanders, and general cryptogenetic infections.

The main point of the study has been to determine the effect of the ammonium oxalate solution upon infected blood. Is this effect deleterious or not? In analyzing our results, many factors must be taken into consideration. A few of the more important ones which will be taken up are the number of organisms in infected blood in various pathological conditions; the viability of different bacteria; the bactericidal effect of the serum introduced into the oxalate solution; the physical appearances of media inoculated with oxalated blood.

Number of Organisms in Infected Blood.—Typhoid fever is a disease associated with relatively few organisms in the circulating blood. Twenty-six positive cultures in this series, representing 190 c. c. of blood, show a total of 172 colonies, an

average of less than one colony per c. c. of blood. Of these twenty-six cultures the highest single count was about three colonies per c. c.; the lowest, one colony from 10 c. c. of blood. The length of time that the disease has lasted seems to be of some consequence, more bacilli being found per c. c. in the earlier stages or relapses than late in the disease. Against the possible objection that the small number of organisms is consequent upon the bactericidal effect of the blood, is the fact that these organisms multiply in defibrinated, oxalated, laked, and clotted blood without the addition of any nutrient medium, as pointed out by Epstein.[1]

One can readily appreciate that in a given sample of blood containing very few organisms or a single bacillus, there is a large element of chance as to whether a medium of the oxalate series or of the control will be favored. In twenty-five cultures in which both methods were used, twenty-one showed growth in some media of each set. Of the remaining four cultures, two showed growth in a single flask of the control series; one was positive in the Conradi medium and a flask of bouillon; and one showed a single colony on a plate and growth in a flask. To offset these four cases, the oxalate method alone was employed on four occasions; each gave a positive result. It is therefore reasonable to suppose that, had all of the blood obtained in the four cases first referred to been introduced into the ammonium oxalate solution, subsequent platings would have shown growth. Apparently that portion of blood used in the oxalate series in these four cases contained no bacilli, and hence the media employed remained sterile.

To emphasize still further the element of chance in transient blood infections and bacteriemias associated with few bacilli, four cases in our series of streptococcemias may be mentioned. Two showed a single colony or a positive flask in the control, the oxalate series remaining negative. Of the other two, one showed three colonies on the plate of the oxalate series, the control media being negative; the other gave a positive

[1] EPSTEIN: *Amer. Jour. of Med. Sciences,* August, 1908.

result in a flask and plate of the oxalate series, four plates and a flask of the control being sterile. Had all of the blood obtained been introduced directly into the oxalate solution, instead of only a portion, the first two cases would have undoubtedly shown growth in the platings. Most of our streptococcus infections recorded in this series have been very intense, and there has been no difficulty or discrepancies encountered in comparing the two methods. A rough average of the cases of post-partum infections shows about sixty colonies per cubic centimeter of blood. Between the two extremes represented by the few bacilli of the typhoid bacteremia and the overwhelming number in some post-partum infections—at times 500 to 900 to the cubic centimeter—all of the other blood infections can be numerically grouped. It has naturally been easier to study the value of the oxalate method in those cases where many organisms were present than when the reverse held true.

Viability of Different Bacteria in the Solution.—This factor is not a negligible one. Most organisms isolated from the blood can be made to grow without difficulty, such, for example, as the typhoid bacillus, Bacterium coli, Bacillus mucosus capsulatus, Micrococcus aureus, and many strains of streptococci and pneumococci. On the other hand, there are various organisms, like atypical pneumococci, the attenuated streptococci associated with endocarditic lesions, and, possibly, the meningococcus and gonococcus, which require extreme care in isolation. The last mentioned organisms we have not encountered in the series under consideration. In general, one has some idea of the identity of the possible infecting agent from the history of the case. Therefore, he can select the most favorable media before distributing the oxalated blood. If this be done, there need be no doubt in most cases concerning a negative finding.

Although our experience with the attenuated organisms found in certain cases of endocarditis has been limited, we have recovered them from the blood oxalate solution in several cases. The attenuated streptococcus grows extremely poorly or not at

all, even on the most favorable media. The studies in the use of ammonium oxalate in cases of subacute and chronic streptococci endocarditis will be published later, when enough cases have been studied.

Bactericidal Effect of Serum Introduced into Oxalate Solution.—The work of Eppenstein and Korte indicates that the typhoid bacillus develops an immunity against the bactericidal action of the blood of the host. Epstein has confirmed this fact. Bacterium coli, Bacillus mucosus capsulatus, most streptococci and pneumococci, Bacillus mallei, Micrococcus aureus and Micrococcus albus are apparently not inhibited by any bactericidal effect of the serum, but tend to multiply in the oxalate solution. Concerning the possible bactericidal effect, we adopted the rough test of inoculating sterile oxalated blood from negative cultures with various organisms. In no instance was a later sub-inoculation from the oxalated blood sterile; in fact, we often employed this method for increasing viability and improving growth in dealing with attenuated organisms. Whether there was originally a bactericidal effect in the fresh blood or not is of no importance here; if it was present it may have been neutralized chemically or by dilution in the ammonium oxalate solution.

In only one instance was there any question as to the exertion of a possible bactericidal effect. This was a case of pneumonia complicating chronic endocarditis. The control media showed an average per cubic centimeter of blood of 4,750 colonies; the oxalate plates (2), which were poured twenty hours after the blood had been obtained, showed only 106 colonies per cubic centimeter of blood. Insufficient blood had been obtained for extended observations, and through a misunderstanding the plates from the oxalated blood were not poured after intervals of one and two hours, as had been intended. Unfortunately, the death of the patient precluded further investigation, so that observations as to the behavior of this particular sample of infected blood over the period up to the twenty-four hour plating, were not possible. While this case is of in-

terest, it does not reflect upon the method; it will be the exception rather than the rule, when the interval between the time the blood is obtained and the time it reaches the laboratory is more than two or three hours.

While conceding a possible bactericidal effect in this particular instance, although the same is quite unlikely, the patient being moribund at the time the blood was obtained, I was, nevertheless, able to recover ample organisms after the twenty-four hour interval to permit of easy diagnosis. This was the only doubtful case; eight others in which the pneumococcus was identified showed either a corresponding number of colonies in the oxalate series as compared to the control, or an increase.

Appearance of Media Inoculated with Oxalated Blood.—Plates properly poured from the blood-oxalate solution after admixture with any nutrient medium present no macroscopic difference from plates poured in the usual way. Briefly summarized, the following data can be regarded as reliable: The phenomena of hemolysis, as produced by the streptococcus, and often by the Micrococcus aureus, are in no way interefered with by the ammonium oxalate solution. Likewise, the appearance of the typhoid "type colony"[1] on the 2 per cent. glucose agar plates of the oxalate series is identical with that on the control plates of the same medium. With the pneumococcus, we have observed hemolysis on some media, and zones of green coloration surrounding the colonies; on others, analogous plates in the two methods presenting identical features. With Bacillus mucosus capsulatus, observations on glucose agar plates as regards the production of zones of green coloration about the deep colonies, and later zones of precipitation, indicate that corresponding phenomena are displayed in the two methods. It is therefore reasonable to assume that with other organisms we may expect to find that the oxalate method will show features in no way different from those seen in blood media poured in the usual way.

Organisms Studied.—The following is the summary of

[1]Epstein: *Proceedings of the New York Pathological Society*, Oct., 1906.

bacteria isolated from eighty-seven positive blood cultures since the oxalate method was introduced:

Bacillus typhosus	29
Streptococcus	26
Pneumococcus	9
Bacillus mucosus capsulatus	7
Streptococcus mucosus capsulatus	1
Micrococcus aureus	5
Bacterium coli	1
Bacillus mallei	2
Attenuated streptococcus	2
Bacillus proteus (atypical)	1
Micrococcus albus	1
Micrococcus zymogenes	1
Mixed infection	2

Effect of Ammonium Oxalate Solution on Various Organisms.—In our study of typhoid infection, it was not uncommon to note an increase in the number of colonies on the glucose plates poured from the oxalated blood.

The streptoccous tends, in most instances, to multiply rapidly in the oxalate solution, the increase at times being several hundred-fold.

While the pneumococcus does not show as marked a multiplication as the streptococcus, in our nine positive infections there was evidence of increase in number of colonies in the majority of instances.

The Micrococcus aureus also tends to multiply in the oxalate solution; the same may be said of Bacterium coli and the Bacillus mucosus capsulatus.

We were fortunate in having for study two blood cultures in two cases of glanders. In the first case there was an increase noted in the number of bacilli, while in the oxalate solution. In the second culture the oxalate series showed fewer colonies, probably due to chance.

In investigating an atypical case of pneumonia the Streptococcus mucosus capsulatus was isolated, the result in the oxalate method was good.

Studies of attenuated streptococci found in cases of sub-

acute endocarditis will be published later. It can be stated here simply that our work thus far indicates that the ammonium oxalate method is satisfactory in such cases.

The Micrococcus albus, Micrococcus aureus, and Bacillus proteus were each studied once. In every instance the organism was readily recovered from the oxalate solution.

The post-mortem blood cultures are of interest. One was a case of suppurative cholangitis from which Bacterium coli was isolated during life; the post-mortem culture showed this organism together with the streptococcus. The other culture taken after death showed three organisms on the plates: Bacterium coli, Micrococcus aureus, and a streptococcus. From these two cases it may be deduced that the oxalate solution will be as serviceable in mixed infections as in the bacteriemias due to a single organism.

Spreads Made from Centrifugalized Oxalated Blood.—In the severe infections a clue to the case may be furnished early by such spreads. We have had some success in these examinations, especially where the streptococcus, pneumococcus, and Micrococcus aureus were the infecting organisms. In the bacteriemias associated with relatively few organisms, e. g., typhoid fever, the examination is necessarily useless.

Conclusions.

Our experience, as detailed above, leads us to believe that it is safe to use the ammonium oxalate method as an intermediate step in blood culture technique. We have shown that good results were obtained with all of the organisms that were encountered during the course of the study. Unfortunately, the meningococcus, gonococcus, and paratyphoid bacilli were not met with, and the Streptococcus mucosus capsulatus was encountered only once.[1] In the study of mixed infections no difficulty

[1]Any experiences which we may have in connection with these organisms will be published later, as will also a comparative study of the value of ammonium oxalate and sodium citrate. Our present experience is decidedly in favor of the former.

should be experienced if the distribution of the oxalated blood is made as soon as the material arrives at the laboratory. The simple method suggested by Epstein as an intermediate step in blood culture work should lead to the more general use in private practice of blood cultures as a diagnostic method.

A STUDY OF THE PATHOLOGICAL ANATOMY OF THE PANCREAS IN NINETY CASES OF DIABETES MELLITUS.

RUSSELL L. CECIL, M.D.

Study of anatomical changes in diabetes mellitus has been limited almost exclusively to lesions which occur in the pancreas. In 1889 were published the well-known experiments of von Mering and Minkowski (1), in which they showed that the removal of the pancreas in dogs produced typical diabetes. The diabetes of depancreatized dogs has suggested that the pancreas furnishes an internal secretion which controls carbohydrate metabolism. Since the other organs of internal secretion are ductless glands, the islands of Langerhans, the only parenchymatous tissue in the pancreas not in communication with the ducts, were associated with pancreatic internal secretion (Laguesse (2), Schafer (3)) at a time when evidence of this association was wanting.

Opie (4), in 1900, described definite pathological changes in the islands of Langerhans in diabetes. These changes consisted most frequently in increase of fibrous tissue within and about the islands. In other cases of diabetes Opie found hyaline degeneration of the islands of Langerhans, occasionally in a pancreas otherwise entirely normal. Opie reaches the conclusion that where diabetes is caused by a lesion of the pancreas, the lesion is of such a character as to injure or destroy the islands of Langerhans. These studies have been followed by a

large number of articles upon the same subject, and some observers have supported, while others have opposed his views. In addition to the lesions described by Opie, other changes in the islands of Langerhans have been noted in association with diabetes mellitus. Schmidt (5) found acute inflammation limited to the interacinar islands in a child ten years old. Ssobolew (6) and others have reported absence of the islands of Langerhans, or great diminution in their number. Hypertrophy of these islands, associated with a peculiar adenoma-like arrangement of their cells, has been described by Reitmann (7), Herxheimer (8), MacCallum (9) and others.

Sauerbeck (10) in 1902 collected from various sources one hundred and seventy-six cases of diabetes in which the condition of the islands had been noted. He found that lesions in the islands of Langerhans had been observed in sixty-two per cent. of the cases.

The present work was undertaken at the suggestion of Dr. Opie, with the hope that the study of a large number of cases by a single observer might furnish accurate information concerning the condition of the pancreas and of the islands of Langerhans in diabetes mellitus. So far as I know, only two of the following cases have been previously reported.

Gross Pathology of the Pancreas in Diabetes.—Of my cases, the pancreas has been described as small or atrophic in only twenty-five per cent. With the exception of this diminution in size, the pancreas exhibited very few notable macroscopic changes. The weight has been given in thirty-six cases, and ranges from thirty to one hundred and eighty-five grammes. The average weight was ninety-four grammes. This is scarcely less than the weight of the normal pancreas, which averages, according to Vierordt, ninety-seven grammes.

In considering the histological pathology of the pancreas in diabetes, it will be convenient to divide the subject into three parts: (1) Changes in the interstitial tissue. (2) Changes in the glandular acini. (3) Changes in the islands of Langerhans.

Changes in the Interstitial Tissue.—Opie (4) has shown

that the interstitial changes which follow obstruction of the duct differ from those observed in connection with diabetes. In the former, sclerosis is chiefly interlobular, and while the lobules may be invaded to a greater or less extent by the newly formed tissue, the progress of the lesion is apparently inward from the periphery of the lobule. In the pancreatitis of diabetes, the reverse is true. The new growth originates between the acini, and interlobular sclerosis, if present at all, is a later phase of the process.

Of the ninety cases which I have studied, sixty-four, or seventy-one per cent., show a definite chronic interacinar pancreatitis. In twenty-one, or twenty-four per cent., the sclerosis is marked. The distribution of this new growth is generally uneven, some lobules being more involved than others. In a number of cases this "focal" sclerosis is conspicuous. Where the induration is advanced, many of the lobules have been largely replaced by fibrous tissue, while the glandular acini which still survive are compressed and distorted, and may give evidence of atrophy. Although the new formed fibrous tissue is often most conspicuous about the vessels and ducts, I have not been able to establish any constant relationship. In many cases, especially where the lesion is mild, the sclerosis seems more advanced in the neighborhood of the islands of Langerhans.

The relation of age to chronic interacinar inflammation is important. The lesion has been entirely absent in all of the four cases under twenty years of age. Between the ages of twenty and thirty, only twenty-five per cent. of cases show interacinar new growth. After thirty, interacinar sclerosis is the rule, being present in ninety per cent. of all cases.

Typical chronic inflammation of the interlobular variety has been observed in only four cases.

An extensive infiltration of lymphoid, eosinophile and plasma cells has been observed very frequently with both types of chronic interstitial pancreatitis. Of the sixty-four cases with interacinar pancreatitis, thirty have shown an abundant cellular infiltration. Lymphoid cells constitute the greater part of this

infiltration, but eosinophile cells and plasma cells are also plentiful. The presence of a considerable number of cellular elements in the stroma would seem to indicate that the inflammatory process was still in the active stage. Polymorphonuclear leucocytes were found in the stroma in greater or less numbers in eight cases, always associated with infiltration of lymphoid cells.

Considerable infiltration of the pancreatic stroma by adipose tissue was found in twenty-six of my cases. Three of these showed a very marked invasion, the lobules as well as many of the acini being widely separated by fatty tissue. In these three cases, the parenchyma appeared much reduced in amount and the sections gave the impression that many acini had been replaced by adipose tissue.

Arteriosclerosis, it is well known, accompanies a large percentage of cases of diabetes. Of my cases, eighty per cent. showed a thickening of the wall of the pancreatic vessels and in half of these cases the vessels were also hyaline. The small arterioles seem to show this change first, and in many instances the lumen of the smaller vessel has been almost entirely obliterated by hyperplasia of the medial coat. Hyaline changes were, moreover, more commonly observed in the small than in the large vessels.

The incidence of arteriosclerosis in diabetes increases rapidly with age. In my series it was present in only forty per cent. of the cases between twenty and thirty years of age, increased to seventy-seven per cent. in cases between thirty and forty, and was present in all but two cases occurring after the fortieth year.

Changes in the Secreting Parenchyma.—Clinically and experimentally, cases are constantly encountered which give no evidence of a disturbance in carbohydrate metabolism, although they show at autopsy extensive destruction of the glandular acini. According to my observations, the most common change of the acini with diabetes is the compression and atrophy, seen in association with the severer types of chronic interacinar pancreatitis. An acinus which has undergone this change is smaller

than the normal; its constituent cells are pressed together and individual cells are ill defined; in some acini a number of the cells have already been destroyed, so that only a part of the original acinus remains. Many acini have been completely obliterated and their place is taken by connective tissue.

Changes in the Islands of Langerhans.—In the ninety cases which I have studied, seventy-nine, or eighty-eight per cent., have shown definite anatomical changes in the islands. By far the commonest lesion was fibrosis, which was observed in seventy-six cases. In forty it was moderate; in thirty-six advanced. In the former cases the islands are surrounded by capsules of fibrous tissue which are thicker than the normal, almost invisible sheaths. The fibrillary coating of the insular capillaries is also definitely increased in thickness, converting the vessels into coarse septa which extend in from the capsule and anastomose at the center of the interacinar island. The cells forming the columns show little or no change in number or appearance.

In the second group of cases the lesions are of a similar nature, but more advanced. The islands of Langerhans are imbedded in dense fibrous tissue which separates them widely from the surrounding alveoli. The intrainsular sclerosis still follows the path of the insular capillaries, the walls of which are several times thicker than the normal. Sections through the center of the body will show an extensive patch of dense fibrous material, rich in spindle cells and sending out broad septa towards the periphery. The cells of the islands are often reduced in number, and appear small and compressed. Occasionally an island of Langerhans is found which has been almost completely converted into fibrous tissue.

Insular sclerosis of the mild type is usually associated with a moderate chronic interacinar pancreatitis, but this relation is not present in all cases. In four of my cases where there was no evidence of a chronic interstitial inflammation, a definite increase of connective tissue was found in the interacinar islands. In these four cases the age varied from twenty-six to seventy

years. Advanced sclerosis of the islands of Langerhans was always associated with considerable interacinar sclerosis, and the insular lesion was always most severe in those areas where the induration was most marked.

The relationship between sclerosis of the islands of Langerhans and arteriosclerosis is of interest. Fibrous changes in the islands are, with few exceptions, associated with a sclerosis of the smaller pancreatic arterioles. Of my cases of insular sclerosis, all but five showed thickening of the vessel walls; in these five cases, no arterial sclerosis was recognizable. Sclerosis of the islands of Langerhans in its early stages is probably a part of more or less generalized arteriosclerosis. It doubtless affects the capillaries of the islands of Langerhans or their afferent vessels and in this respect resembles the beginning fibrous changes in the glomeruli of the kidney. When the process is advanced, chronic interacinar inflammation is always present and the entire interstitial framework of the island becomes involved in the new growth. The insular capillaries, however, still bear the brunt of the attack.

Hyaline degeneration of the islands of Langerhans is the lesion which has occurred next in frequency to sclerosis, being present in twenty-seven cases (thirty per cent.). In most instances it has been associated with sclerosis of the pancreatic vessels and of the islands of Langerhans. In six cases with hyaline changes in the interacinar islands there was no increase in the interacinar connective tissue. As a rule the majority of the islands of Langerhans were affected, but in a few cases only an occasional island showed the change. The hyaline material is first deposited along the capillaries of the island, separating the latter from the cells. As the process advances, it extends outward. Many of the cells are replaced by the hyaline substance, and those which still survive are often compressed and atrophic. Eventually, the entire area of the island may be occupied by homogeneous hyaline material. The nuclei of the endothelial cells appear to persist longest, but finally these, too, are destroyed.

I have found hyaline degeneration of the islands of Langerhans in only two of the cases under thirty years of age. It appears to be most common after the fifth decade. In my cases I have found that this lesion was, with the exception of one case, always associated with diabetes of more than one year's duration. The average duration of the diabetes in sixteen cases with hyaline islands was three years and six months.

In nine cases I have observed a well-marked infiltration of leucocytes about the islands of Langerhans. A more or less general infiltration of the same character sometimes accompanied this lesion, but the cells were more numerous and concentrated in the vicinity of the interacinar islands. The cells were generally arranged in the form of a halo about the island of Langerhans just outside of the capsule, though in some cases the island itself was invaded. The average duration of the diabetes in the six cases of this group where the duration was definitely stated was only eleven months.

Hypertrophy of the Islands of Langerhans.—Laguesse (2) found that the islands of Langerhans in the normal pancreas of man varied from one hundred to four hundred microns in diameter. Islands of Langerhans exceeding four hundred microns were very rare. Lydia Dewitt (11) measured these bodies in the human pancreas, and found that they averaged .0153 c.mm. in volume. In her measurements the diameter never reached 400 microns. The pancreas in thirty-eight per cent. of my cases showed islands of Langerhans which equalled or exceeded 400 microns in diameter. Round or ovoid islands were selected and the long diameter was measured.

In one case an island of Langerhans was found which measured seven or eight hundred micromillimeters—a diameter about four times that of normal. In the cases where giant islands were found, the average size of the interacinar islands was increased. Hyaline degeneration of the islands was associated with about a third of the cases with hypertrophy and it was observed that hypertrophied islands, as a rule, were free from hyaline material, or contained it in only small amounts.

Reitmann (7), Herxheimer (8), MacCallum (9) and others have described a peculiar form of hypertrophy of the interacinar islands, which they have encountered in the pancreas of some cases of diabetes. The cells displayed, instead of their usual arrangement in irregular cords or masses, a definite columnar arrangement, and were often grouped together in circular cords about capillaries. In seven of our cases, a similar lesion has been observed. The islands of Langerhans are considerably larger than the normal, some of them reaching a diameter of seven or eight hundred microns. Their contour is quite irregular; loops and cords of columnar epithelial cells push their way out between the adjacent acini, and, but for differences in staining reaction, might possibly be mistaken for normal glandular structure. In six of these cases, hypertrophy of the islands of Langerhans was associated with increase of fibrous tissue about the insular capillaries.

Diminution in the number of islands of Langerhans was a common finding. While there was no instance in my series of a pancreas entirely devoid of islands of Langerhans there were a number of specimens in which they were exceedingly few.

Several writers have found an absence or scarcity of islands in diabetes. Ssobolew (6) reported fifteen cases in which the islands were either absent altogether or were much diminished in number. Two factors probably contribute to explain this diminution. First, there is a group of cases in which the pancreas may show little or no change, and where the condition is perhaps due to a congenital defect. Opie reports the case of a child, fourteen years old, with hereditary diabetes, in which the number of islands showed a well-marked diminution. In a second group of cases, the scarcity of islands of Langerhans is associated with chronic interacinar pancreatitis of severe type. Here the islands are probably destroyed and their places occupied by fibrous tissue.

In twenty of my cases the islands of Langerhans showed a marked diminution in number, recognizable by inspection of sections. These cases may be classified as follows: (1) Scarcity

of islands in a normal pancreas (5 cases); (2) Scarcity of islands in association with chronic interacinar pancreatitis (15 cases).

Cases in Which the Pancreas was Normal.—Eleven of my cases showed no discoverable anatomical lesion in the pancreas. The pancreas in two cases of this group was described as small, but in all other respects the gross appearance agreed with the microscopic in suggesting no pathological changes. In five cases diminution in the number of interacinar islands was marked. The islands were of small size in five cases. The age in all but one of these cases was under thirty-five years.

Relationship of Diabetes to Organs other than the Pancreas.—*Cirrhosis of the liver* was present in seven of my cases. The pancreas from all of these cases showed well-marked chronic interacinar inflammation, which in two instances was far advanced. One etiological factor is probably active in both organs. The same statement is perhaps applicable to chronic nephritis, which was present in twenty-five cases, and was in all instances associated with more or less advanced chronic inflammation of the pancreas.

Two cases of cirrhosis of the liver were accompanied by *hemochromatosis*. This remarkable disturbance of iron metabolism was first described by von Recklinghausen (12), and is characterized by a deposition of a brown iron-containing pigment in the various tissues and organs of the body. Hemochromatosis with diabetes or "Bronzed diabetes" is well recognized. Von Recklinghausen found cirrhosis of the liver a constant feature of the disease, and more recently a number of writers have noted the occurrence of chronic interstitial pancreatitis.

Case XLII was obtained through the kindness of Dr. MacCallum of the Johns Hopkins Hospital. A man, thirty-seven years of age, gave a history of diabetes of nine months' duration. The urine contained 6.5 per cent. of glucose. Acetone and diacetic acid were also present. There were ascites and pigmentation of the skin. The patient died in coma. At autopsy, marked pigmentation was found in the liver, heart, pancreas, lymph glands and skin. The liver showed cirrhosis and the heart was hypertrophied. The

pancreas was large and firm and weighed 150 grams. On section it was brown, and mottled with fat. Microscopically, there is a very marked infiltration of fat tissue which appears to have replaced the glandular structures in many places. This invasion is not confined to the interlobular tissue, but separates the acini as well. There is also a definite new growth of connective tissue between the acini, which is rich in spindle cells and infiltrated with a moderate number of lymphoid and plasma cells. The interstitial tissue is the seat of an abundant deposition of light brown pigment which reacts positively to the chemical test for iron. Many of the acinar cells are loaded with this pigment. Some of the acini are considerably swollen, and their cells stain faintly. The walls of the blood vessels are not appreciably thickened.

The islands of Langerhans are very scarce, and considerably smaller than the normal, none of them measuring over 200 microns in diameter. The fibrous capsules about the islands are thickened, and infiltrated by pigment. Some of the island cells also contain pigment, but the remainder take their usual stain.

Case LIX was obtained through the kindness of Dr. Wright of the Massachusetts General Hospital. A man forty-five years of age had had three per cent. of glucose in his urine, as well as acetone and diacetic acid. The patient died in coma, and at autopsy there were found cirrhosis of the liver and pigmentation of the liver and pancreas. The pancreas was dark brown in color and rather soft.

Microscopically, sections from the pancreas show a marked new growth of connective tissue between the acini. The lobules are widely separated by adipose tissue. The stroma is the seat of a universal deposition of iron pigment which stains blue with ferrocyanid of potassium and hydrochloric acid. Many of the acinar cells are also loaded with pigment. The walls of the blood-vessels are somewhat thickened. Dense collections of lymphoid and polymorphonuclear cells are found in the neighborhood of the larger ducts. The islands of Langerhans are fairly numerous and normal in size, many of them are surrounded by dense capsules of fibrous tissue, and the insular capillaries are thickened. A considerable number of insular cells are distended with pigment, and give evidence of degeneration, the nuclei staining indistinctly.

The islands in these two cases show very similar lesions, namely, encapsulation by fibrous tissue and a deposition of iron pigment in the insular cells. In the case first described there was a marked diminution in the number of the islands of Langerhans, probably partly due to the advanced lipomatosis.

The association of diabetes with certain diseases of the ductless glands has been frequently observed. Hansemann (19) collected from the literature of the subject fifteen cases of *ex-*

ophthalmic goiter which had been accompanied by diabetes, but there had been no opportunity to study the pancreas. A number of other writers have more recently observed glycosuria in connection with Graves' disease. Falta, Eppinger and Budinger (16) have studied the relationship between the pancreas and the ductless glands,—more particularly the thyroid and suprarenal glands. By removing one or more of these organs and observing the effect in metabolism, they claim to have established a definite relation between the three organs.

I have been able to include in the present series one case of diabetes which was associated with exophthalmic goiter. The case was reported by Dr. Morris Manges in the *Mt. Sinai Hospital Reports,* Vol. II. Dr. Libman was kind enough to supply me with a part of the pancreas.

The patient, a woman, forty years of age, gave a history of diabetes of six months' duration, her chief complaint being weakness, emaciation and thirst. The urine contained five per cent. of glucose. Acidosis was present. There were marked exophthalmos, tachycardia and neuralgic pains. The latter were relieved by thyroid extract. Death occurred from asthenia and cardiac failure. At autopsy the thyroid gland was enlarged and firm; microscopically there were glandular hyperplasia and chronic inflammation. The pancreas was atrophic and weighed 45 grams; on section it was pale and soft.

Microscopically the pancreas exhibits typical chronic interacinar pancreatitis of advanced grade. The acini are small, and separated by dense fibrous tissue, which in some places has almost completely replaced the parenchyma. The stroma shows rich infiltration by lymphoid and plasma cells, with a few polymorphonuclear leucocytes. The vessel walls are thickened and hyaline. Islands of Langerhans are fairly numerous, but have small area. In places where the sclerosis is severe the interacinar islands are much involved, being buried in dense fibrous tissue and invaded by the same material. Many of them have been almost obliterated by the fibrous hyperplasia.

Adenoma of the thyroid gland has been noted in the anatomical diagnosis in two of my cases with diabetes (Cases XXIX and XXXIV). It is a significant fact in this connection that in both cases the adenoma-like hypertrophy of the islands of Langerhans, described above, is present. In Cases XXIX this hypertrophy affects nearly all the islands of Langerhans, which

often attain great size. In Case XXXIV the insular hypertrophy is also well marked. The pancreas in both of these cases shows a well-marked chronic interacinar inflammation with considerable increase of fibrous tissue in and about the islands of Langerhans.

Myxedema was found associated with diabetes in one of my cases (Case VI).

The patient, a woman, seventy-four years of age, was first admitted to the Presbyterian Hospital on March 12, 1899, complaining of weakness, shortness of breath, despondency, and gradual loss of mental powers.

There was a general thickening of the subcutaneous tissue. The skin was dry and scaly, and the nails and hair were brittle. There was puffiness under the eyes, and the tongue was thickened. Speech was deliberate and lisping in character. Pulse tension was high. At this time there was no glucose in the urine. The patient was treated with thyroid extract and improved rapidly.

A year and a half later, the patient was admitted again to the hospital complaining of thirst, polyuria, puritus vulvæ and eczema. Myxedema was much improved. The urine contained four per cent. of glucose. The amount of sugar diminished under treatment. During the two years following, the patient was in the hospital several times, and finally died in coma September 6, 1902.

At autopsy the thyroid weighed only eight and a half grams; microscopically there is very advanced atrophy of the parenchyma. The alveoli have been almost completely obliterated and their places are occupied by fibrous tissue, densely infiltrated in places by lymphoid cells.

The pancreas weighed 120 grams, and was of tough consistency. Microscopically, advanced chronic interacinar inflammation, and universal infiltration of adipose tissue can be recognized in spite of extensive postmortem digestion. The islands can be identified and show considerable sclerosis.

The occurrence of glycosuria with *acromegaly* has been observed in a considerable proportion of cases of this disease. Hansemann (19) and others have described such cases in which a chronic interstitial pancreatitis was found. Through the kindness of Dr. Norris I have been able to study the pancreas from a case of acromegaly which was accompanied by diabetes.

The case was reported by Dr. Norris in the *Proceedings of the New York Pathological Society*, February, 1907, and is the only case of acromegaly in which the condition of the islands has been described.

The patient, a man, thirty-three years old, was admitted to Bellevue Hospital with the following symptoms: Progressive enlargement of jaw, nose, ears, hands and feet. Persistent frontal headaches, and attacks of vertigo. Gradually increasing loss of vision, ending in atrophy of both optic nerves and almost complete blindness. There were recurrent epileptiform attacks. Glycosuria had been present during twenty-two months.

At autopsy, a large tumor was found, connected by a broad pedicle to the pituitary gland which was itself enlarged; microscopically, the tumor is composed of cuboidal or oval cells which are arranged in irregular alveoli. The stroma is very scanty. The alveoli are separated by capillaries, whose endothelial lining is apparently in direct contact with the alveolar cells. In some places the capillaries are dilated, giving the tumor a very vascular appearance.

The pancreas was large and firm, and weighed 170 grams. The lobulation was distinct and no macroscopic lesions were noted.

Microscopically, the pancreas is free from interstitial induration. There has been some post-mortem digestion in a few places, but otherwise the glandular acini are normal in appearance. The walls of the blood-vessels are slightly thickened. The islands of Langerhans are numerous, irregular in outline, and larger than the normal. One island is found which measures six hundred micromilimeters in diameter. Some of the larger islands present a very unusual appearance. The insular cells are large, and often columnar in shape and arrangement. In many instances the cords of cells form partial or complete circles, whose lumina contain the insular capillaries. These capillaries show definite sclerosis. There is a marked deposit of hyaline material in a few of the islands of Langerhans.

The coexistence of this adenoma-like hypertrophy of the islands of Langerhans with adenoma of the pituitary gland is especially significant if it be borne in mind that the same type of insular hypertrophy was observed in association with the two cases of adenoma of the thyroid gland; at present I can offer no satisfactory explanation of this association.

Other anatomical changes associated with diabetes are of considerable interest.

Gangrene is a common complication, and is generally attributed to two causes, arteriosclerosis and lowered resistance in the tissue, resulting from the diabetes. Gangrene occurred in sixteen of my cases and was in all instances associated with arteriosclerosis and well marked chronic interacinar pancreatitis.

In the present study of the pancreas from ninety cases of diabetes, the following pancreatic changes have been encountered:

1. Chronic Inflammation of the Pancreas.
   - Interacinar pancreatitis, sclerosis of islands of Langerhans..... 39
   - Interlobular pancreatitis, sclerosis of islands of Langerhans..... 4
   - Interacinar pancreatitis, hyaline degeneration of islands of Langerhans 19
   - Interacinar pancreatitis with lipomatosis; sclerosis of islands of Langerhans 2
   - Interacinar pancreatitis, with lipomatosis, hyaline degeneration of islands of Langerhans 1
   - Interacinar pancreatitis, with siderosis of islands of Langerhans (Hemochromatosis) 2

2. Parenchyma normal; Lesions of the Islands of Langerhans.
   - Sclerosis of the islands of Langerhans..... 4
   - Hyaline degeneration of the islands of Langerhans..... 7
   - Infiltration of leucocytes about islands of Langerhans..... 1

3. Pancreas normal 11

90

Of the eleven cases of normal pancreas, five showed a marked diminution in the number of islands of Langerhans. In two other cases the pancreas was abnormally small.

Conclusions.

1. Anatomical lesions of the pancreas occur in more than seven-eighths of all cases of diabetes mellitus.

2. In diabetes associated with lesions of the pancreas, the islands of Langerhans constantly show pathological changes (sclerosis, hyaline degeneration, infiltration of leucocytes and hypertrophy).

3. In some cases of pancreatic diabetes (twelve of ninety cases) the lesion of the pancreas is limited to the islands of Langerhans.

4. In sixteen cases of diabetes associated with hyaline degeneration of the islands of Langerhans the average duration of the disease has been three and a half years. In six cases of diabetes associated with an infiltration of leucocytes about the islands of Langerhans the average duration has been eleven months.

5. Destructive lesions of the islands of Langerhans may be associated with compensatory hypertrophy of other interacinar islands.

6. Peculiar adenoma-like hypertrophy of the islands of Langerhans occurs in a small proportion of cases (seven of ninety) and may be associated with adenomata of the thyroid gland (two cases) and of the pituitary body (one case).

7. Diabetes mellitus occurring in association with hemochromatosis (bronzed diabetes) is referable to pigmentation and destruction of the islands of Langerhans.

8. The pancreas is found to exhibit no pathological changes in twelve per cent. of cases. In approximately one-half of these cases it has been noted that the size of the gland or the number of islands is much less than normal.

9. Fifty per cent. of cases of diabetes mellitus occurring before the age of thirty years are associated with lesions of the pancreas; seventy-five per cent. of all cases of diabetes in which the pancreas is normal occur before the age of thirty years; ninety-seven per cent. of cases of diabetes occurring after the age of thirty years are associated with lesions of the pancreas; and eighty-six per cent. occur in association with chronic interacinar pancreatitis accompanying arteriosclerosis.

10. Interacinar pancreatitis which occurs in seventy-three per cent. of all cases of diabetes is almost constantly associated with arteriosclerosis; gangrene of the extremities, which occurs with one-fourth of all cases of interacinar pancreatitis, is doubtless referable to the same cause.

11. Chronic interlobular pancreatitis, when associated with diabetes, is accompanied by sclerosis or hyaline degeneration of the islands of Langerhans.

12. Diabetes in association with myxedema or with exophthalmic goiter may be referable to a lesion of the pancreas, namely, chronic interacinar inflammation with sclerosis of the islands of Langerhans; diabetes in association with acromegaly may be referable to a lesion of the islands of Langerhans, namely, sclerosis and hyaline degeneration with adenoma-like hypertrophy.

In closing I wish to express my gratitude to Dr. Opie for much assistance and many valuable suggestions. I am indebted

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Discussion.

Dr. Harlow Brooks called Dr. Cecil's attention to the fact that he had described lesions in the islands of Langerhans in cases of acromegaly over ten years ago, one of which was a case of bronze diabetes. He thought that it was the general feeling that, while the islands of Langerhans were diseased in diabetes with remarkable constancy, still many marked lesions occurred in the islands quite independent of diabetes. He himself had never seen the parenchymatous changes so beautifully described by Dr. Cecil, but the other changes were seen with considerable constancy without diabetes.

Dr. James Ewing said that he believed this report contained the largest proportion of cases with lesions of the islands of Langerhans yet recorded in connection with diabetes. In a considerable proportion of the cases the lesions found were those of the first group and were chiefly limited to the capsule of the islands. He would like to know if it were possible that such lesions could be sharply separated from those in the interstitial tissue. He had been interested in cases showing chiefly dilatation of the ducts and alveoli of the pancreatic parenchyma, lesions which were not illustrated in the sections shown.

Dr. Charles Norris thanked Dr. Cecil for his able paper; he considered that his opinion was extremely valuable. His own experience had been confined to the examination of the pancreas in four cases of diabetes, but in all these he had seen hyaline changes in the islands of Langerhans. These changes were also present in cases of acromegaly, and were the only changes which were present. In the routine work at Bellevue Hospital, however, they saw constantly a large number of pancreases which showed more or less inter- as well as intralobular pancreatitis, without lesions of the islands of Langerhans and not associated with diabetes. In a large number of cases with arteriosclerosis there were also changes in the pancreatic vessels. In view of these facts, it would seem that these lesions were merely associated or frequently found in diabetes, and therefore not causative.

Dr. Theodore C. Janeway said that one great flaw in the explanations of the relation of pancreatic lesions to diabetes was the entire lack of any parallelism which most observers have noted between the severity of the disease and the extent of the anatomical lesions of the pancreas. He had seen four cases of normal pancreas associated with rapidly fatal diabetes. The most severe and most rapidly fatal diabetes was most frequently found associated with a normal pancreas; whereas the most pronounced changes were found in cases of diabetes occurring in older persons in whom such changes are more common apart from diabetes. There could be no question that there was a relation of some kind between the pancreas and the carbohydrate metabolism and diabetes; but the relation did not run in any way parallel with the course of the severity of the disease, was evidently a very complex one, and could not be solved by further anatomical studies of the pancreas, but must be reached from another side entirely.

Dr. E. Libman drew attention to one case, material from which he was under the impression he had given to Dr. Cecil. In that case there was marked hemosiderosis in the liver and spleen. In the pancreas there was no hemosiderosis, but there

was hyaline degeneration of the islands of Langerhans. The case was different from the type described by Dr. Opie in which there was hemosiderosis of the pancreas also, and in which he believed that the secondary changes resulting from the pigmentation were the cause of the diabetes.

Dr. Cecil acknowledged his error as pointed out by Dr. Brooks. He said that, while lesions were very often found in the pancreas in cases which were not diabetes, these lesions were not found in the islands. He did not think that marked lesions of this sort were often found outside of diabetes. In regard to the large percentage of sclerotic islands noted, he had divided these into two groups: those in which the sclerosis was marked, and those in which it was not. Of course, in the latter group there would be a question whether the lesion was sufficient to interfere with the function of the islands. Thirty per cent. of his cases showed hyaline degeneration of the islands. There were certainly a number of cases included in the sclerotic group in which the lesions must be spoken of as moderate. He had not seen any dilatation of the alveoli except in one case, in a young woman about thirty-six years of age. In regard to the relation between the extent of the lesion and the severity of the disease, Dr. Cecil said that his clinical data were rather meager, and it had been hard to determine just how severe the diabetes had been; but he had found, as Dr. Janeway had said, that very often patients with an apparently normal pancreas, or with the least changes, ran a rapid course, and that with cases in older people where the lesions were more severe the course of the disease was longer.

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